Finel

INFLAMMATION

INFLAMMATION

AN INTRODUCTION TO THE STUDY OF PATHOLOGY

BEING THE REPRINT (REVISED AND ENLARGED)
OF AN ARTICLE IN PROFESSOR ALLBUTT'S
'SYSTEM OF MEDICINE'

BY

J. GEORGE ADAMI, M.A., M.D., F.R.S.

SOMETIME FELLOW OF JESUS COLLEGE, CAMBRIDGE
PROFESSOR OF PATHOLOGY, M'GILL UNIVERSITY, MONTREAL

London
MACMILLAN AND CO., LIMITED
NEW YORK: THE MACMILLAN COMPANY
1907

First Edition, Allbutt's "System of Medicine," Vol. I., 1896
Second Edition, ,, ,, ,, ,, 1905.
Third Edition, January 1907.

PREFACE

The development of a science resembles strikingly that of the individual intelligence. Your child, once he begins to perceive, passes into the stage of perpetual "why?" He is not satisfied with the recognition of phenomena, but would know from his elders how they come about. It is deserving of note that at first those explanations satisfy him that appeal to the imagination rather than to the reason. He is not prepared to appreciate and to accept mathematical proof; he lives in fairyland. Gradually his powers of reasoning become developed, but this under the guidance of his elders and teachers, and for long, while still seeking explanations, he accepts those given to him. There are those who never pass beyond this stage of deference to authority. But some, at least, as manhood approaches, begin to think for themselves; begin to see that the explanations given by their elders are not all of them adequate, nor all satisfactory; and so is reached the stage of youthful *Sturm und Drang*, during which period the brighter spirits, heedless of authority, in the exuberance of youthful imagination, proceed impatiently to weave and elaborate explanations of their own. It may be that, despite their little experience and the fewness of the facts on

which they base themselves, they light upon truths of wide scope. But too often it happens at this period that inadequate hypotheses are light-heartedly imagined and given to the world. During this period hypothesis after hypothesis may be enunciated only to be found wanting. As manhood is entered into, the individual learns that it is not essential to discover an immediate explanation for everything, and now begins patiently to accumulate data in the hope that wider experience and fuller command of facts will eventually afford material for the right solution of a given problem. Thus at last, with the necessary experience, maturity and ripe powers of reasoning are attained.

Pathology has passed through all these stages: through its infancy, in which medicine men and priests and augurs explained disease by fables; through a long childhood of deference to Galenistic authority; through a stormy youth of wild theorising and advocacy of system after system — iatro-chemical, iatro-mechanical, Brunonian, and many another; through a period of reaction to the same, led by Virchow (extending roughly during the fifty years between 1845 and 1895), and now it may be said to have reached the age of maturity. There are those conscientious workers who continue to maintain that it is immature; who hold that we have not passed the stage of working hypotheses as distinct from established theories; who lay down that it is our duty still sedulously to accumulate facts without venturing to draw broad conclusions from the same. This, we think, is a mistaken opinion. There are, it is true, many territories which remain imperfectly explored;

but there are others which have been worked over so abundantly and have yielded so vast a harvest of facts, that unless we proceed to marshal these facts into order, and to classify them in due relationship one to the other, the danger is imminent that the accumulation becomes a very chaos; that workers in one part of the territory, ignorant of the experience and material gained by those in another, will not merely waste their energy but work at cross purposes. In short, pathology will become a scientific Babel. The danger, indeed, is already with us; we find sundry surgeons enunciating a pathology that is at variance with that of the physicians. Already in some countries, through a divorce between general pathology and bacteriology, there is a lack of eagerness on the part of the workers in the former to accept the data afforded by the latter; and so huge has become our subject that no one man can have an equal familiarity with the recent advances in neuropathology, hæmatology, teratology, and ante-natal pathology, immunity and the study of infection.

This being so, it is urgent that some of those interested in medicine should give their time and energy not so much to the development of any one particular field as to collecting and arranging the main data bearing upon the causes and development of morbid conditions, and the establishment of the deductions which may reasonably be gained therefrom. If with each passing year it is becoming less and less possible for any one individual to have a familiarity with every branch of pathology, the time has come to provide a common basis of facts and theory which is acceptable to and accepted

by the workers in various branches, thereby ensuring an orderly development of the science of medicine in its many departments, a development which, starting from a common base, shall be harmonious.

Such common basis is more particularly afforded by the data gained through researches into the process of inflammation. It cannot be too strongly emphasised that *a knowledge of the inflammatory process is the foundation of all pathology.* We see that ultimately all disease is due to the disturbance of the relationship and equilibrium between the organism and its surroundings; from the point of view of the organism every such disturbance causes injury, provided that the local resources are not sufficient to counterbalance it forthwith. If we accept the definition laid down at the beginning of this article, viz. that (briefly) inflammation is the local reaction to injury, it follows that we must first gain a knowledge of what constitutes the inflammatory process if we are to understand disease of all orders. Even if certain diseases are not local conditions but general, affecting to a greater or less extent the whole organism, nevertheless such general conditions are but the summation of a series of local disturbances, and must have originated from one or more local disturbance; to master the general we must first understand the particular and the local.

Thus, if our pathology is to be not a mere *catalogue raisonnée* of names of morbid states, with precise descriptions of what those names indicate, but is to be a science—or, in other words, an endeavour to bring into order and relationship the phenomena of disease, and,

recognising the relationship between phenomena, to deduce the laws which underlie and determine the individual cases of diseases—then, obviously, the study of the inflammatory process is the natural starting-point for a right understanding of that science and what it can teach us.

These considerations governed my treatment of the subject when, ten years ago, I was invited by Professor Allbutt to write the article on Inflammation for his new *System of Medicine*. I strove then to bring together all the data known to me bearing upon the subject of the reaction to local injury, and, cutting myself free from all the schools and established doctrines, I endeavoured conscientiously to select those facts which could not be gainsaid, and to draw from them the deductions which seemed most rational. There was here no attempt to bring forward anything that was new or that had not been already recognised by individual workers. At most it might be said that many of the facts brought forward, as also the method of approaching the subject, were new to the text-books. It has been a source of profound gratification that this article has from so many sources been accepted as authoritative, and that, when nine years later I came to revise it in the light of the abundant observations which had been published in the meantime, while there was much that might be added in amplification, there was little to correct. The teaching which in 1896 was to a certain extent novel is now in 1906 widely accepted. The revised article is here printed in book form in the hope that it may prove serviceable to the practitioner wishing to keep abreast of recent

developments, and to the medical student who cannot be expected to purchase the large volumes of Professor Allbutt's *System*. And printing it thus I have to express my appreciation of the favour extended to me by Messrs. Macmillan and Co. in departing from custom and publishing as a separate entity what is portion of one of their larger works.

In republishing it thus I have taken the opportunity to render it more complete and seasonable. The present great interest shown in Sir A. E. Wright's brilliant researches upon opsonins demands that his observations obtain fuller description (though not fuller appreciation) than was accorded by me a year ago. Professor Bier's treatment of inflammation by induced hyperæmia has likewise aroused widespread attention. The essentials of that treatment are here described, and I have been led to add what it is trusted will be a useful chapter on the application of the principles laid down in this work to the treatment of inflammatory states. It has seemed useful also to reintroduce in a modified form the paragraphs upon the hæmal leucocytes which, present in the first, were omitted in the second edition of the article in Professor Allbutt's *System*, being there more properly treated in a new article upon the blood; and doing this, to call attention to the advances gained by Schridde through the employment of methods which permit the differentiation of the various forms of leucocytes within the tissues.

Montreal, *December* 1906.

CONTENTS

PART I

A GENERAL SURVEY OF THE PROCESS OF INFLAMMATION

CHAPTER I

CHAPTER II

CHAPTER III

CHAPTER IV

CHAPTER V

CHAPTER VI

CHAPTER VII

PART II

THE FACTORS IN THE INFLAMMATORY PROCESS

I. THE PART PLAYED BY THE LEUCOCYTES

CHAPTER VIII

CHAPTER IX

CHAPTER X

CHAPTER XI

CHAPTER XII

CHAPTER XIII

CHAPTER XIV

CHAPTER XV

II. THE INFLAMMATORY EXUDATE

CHAPTER XVI

CHAPTER XVII

III. THE BLOOD-VESSELS

CHAPTER XVIII

CHAPTER XIX

IV. THE NERVOUS SYSTEM

CHAPTER XX

V. THE CELLS OF THE TISSUES

CHAPTER XXI

CHAPTER XXII

CHAPTER XXIII

VI. TEMPERATURE CHANGES

CHAPTER XXIV

PART III

GENERAL CONSIDERATIONS

CHAPTER XXV

CHAPTER XXVI

CHAPTER XXVII

CHAPTER XXVIII

PART I

A GENERAL SURVEY OF THE PROCESS OF INFLAMMATION

CHAPTER I

PROVISIONAL DEFINITION

It is usual to begin the description of a morbid process by defining that process. In the case of inflammation, however, we have to deal with a process so complex, so modified by modifications of the many factors involved, and so variable in its manifestations according to the variety of its causes and the region of incidence, that the attempt to define it has proved a pitfall to pathologist after pathologist; moreover, to advance a definition of the process at the beginning of this article in terms differing to any considerable extent from those employed by previous writers, would demand a criticism of the many previous attempts; and in order that the definition put forward be duly supported, would necessitate an essay covering the whole field about to be traversed.

Use of the Name.—Yet, in the meantime, inasmuch as divergent views are held of the limitations of the use of the name inflammation, a few words of introduction are advisable.

Two courses are before us: either to employ the name strictly in accordance with the primitive definition, and thus only to include as cases of inflammation those states in which there are present redness, swelling, heat, and pain, rigidly excluding all cases in which these cardinal symptoms are not present; or, on the other hand,

departing from tradition, to include as inflammations all those morbid proeesses whieh seem to have a cause and progress inseparable from and merging into the cause and progress of the state charaeterised by the classieal symptoms. The first eourse is impossible; it is as though one were to declare that red phosphorus is not phosphorus beeause in externals generally it does not agree with the definition of the yellow form made years before the allotropic modification was diseovered. We are now well agreed that of the classieal symptoms, one, two, or three may be unreeognisable, and in fact absent; and yet the condition of inflammation be undoubtedly present.[1]

The seeond is the only possible eourse, that, namely, whieh assoeiates all those states which under suitable eonditions may result in the production of the four classieal symptoms, and, moreover, originate from a common eause. Holding this view, it will in the meantime be well for me, in order to afford a starting-point for the deseription and discussion of the subjeet, to seleet from the many definitions one whieh is based not on symptomatology, but upon etiology, and indieates a common origin for all eases of inflammation. I would first note that which in this eountry has reeeived the most eordial support, the definition given by the late Sir J. Burdon-Sanderson (1) in his well-known artiele in Holmes' *System of Surgery*: "The proeess of inflammation is the sueeession of ehanges whieh oeeurs in a living tissue when it is injured, provided

[1] A course allied to this has found favour of late years among some surgical pathologists, who, with Hüter (2), would limit the use of the term to those cases and those only in which the classical symptoms, or the majority thereof, are present and associated with suppuration,—they urge with Zahn (3) that inflammation only occurs when pyogenetic micro-organisms are present, and state that when a wound heals aseptically it heals without inflammation. This modified course is equally impossible; pyogenesis must not be confounded with inflammation.

that the injury is not of such a degree as at once to destroy its structure and vitality." This definition includes too much. The hæmorrhage that occurs in the liver when it is injured, and the changes that there occur in the extravasated red corpuscles, are scarcely to be classed among inflammatory phenomena; the atrophic changes which occur in the retina, when through injury it becomes detached, are due mainly to malposition and disuse rather than to the primary trauma. Grawitz (4) has put forward a definition based upon the same fundamental conception, but so worded as to exclude largely, if not wholly, the above objections; for, as regards the second, it may justly be urged that atrophic changes are not reactive, but due to lack of reaction. Inflammation, he holds, *is the reaction of irritated and damaged tissues which still retain vitality.* Either of these definitions has this great advantage, that, stating the cause, it clearly recognises inflammation as a *process* and not as a *state.* The manifestations of this process under favourable conditions—where the region injured is a loose and vascular tissue, and where the injury is sufficiently severe or extensive—are redness, swelling, heat, and pain: *redness* from the congestion of the vessels; *swelling* from the exudation of fluid and corpuscles from the congested vessels; *heat* from the increased amount of blood in the region, and *pain* from the irritation of the terminations of the nerves in the region. To these four symptoms may be added a fifth, *disturbance of function* brought about by this departure from the normal condition of the region. Under unfavourable conditions—where the region injured is dense or less vascular, or where the injury is less severe—one or all of these symptoms may seem wanting; nevertheless a minute examination of the tissues will show the same succession of changes as in the former case.

CHAPTER II

THE COMPARATIVE PATHOLOGY OF INFLAMMATION

Accepting, then, this working definition, in order to arrive at a due comprehension of the succession of changes which we take to constitute the inflammatory process, it will be well with Metchnikoff[1] (5) to institute a series of observations upon the reaction to injury exhibited throughout the animal kingdom from the lowest forms upwards to man. By this means we shall be enabled to determine what factors in the reactive process are from their constancy of primary importance; what are common and essential, and what are superadded in the higher animals.

The Response to Injury among the Protozoa.—Beginning our study with the lowest and simplest forms of life —forms so lowly that they have been regarded both as animals and as plants—we find even here phenomena accompanying the reaction to injury which throw light upon the inflammatory process as seen in the higher animals. Taking as an example the amœba, we find, in the first

[1] The succeeding paragraphs are of necessity very largely an epitome of sundry portions of Metchnikoff's most pregnant work upon the comparative pathology of inflammation. By comparing them with the work in question, it will, however, be seen that they depart from it in several points; more especially in dwelling upon the extracellular—excretory—activities of the wandering cells, and in bringing more prominently forward the response to injury on the part of the fixed cells.

place, that the nucleus plays an important part in this reaction. If, as Metchnikoff has shown, one of the larger amœbæ be cut in two, the region of injury becomes rapidly indistinguishable—the protoplasm of each moiety closes up, leaving no mark or scar: but of the two parts that which retains the nucleus grows and proliferates; the other disintegrates in a longer or shorter time. As I have shown in a recent address (6), from every consideration we are forced to regard the nucleus as the dominant constituent of the cell, controlling its higher activities; the nucleus is essential for continued growth and for reproduction. Or injury may induce changes in the protoplasm of the entire amœba: thus Miss Greenwood (7) points out that, without necessarily bringing about death, the interrupted current or an aqueous solution of thymol leads to a process of exudation or extrusion of clear hyaline spheres, or of spheres holding crystals and granules, from the surface of the organism—a process resembling that occasionally seen in the cells of an inflammatory area in higher animals. Nor is this all; apart from changes in the structure of these unicellular animals, differences may be seen in the behaviour of amœbæ towards foreign bodies. It would seem, according to Le Dantec (8), that amœbæ ingest non-irritating foreign substances indifferently, provided they be sufficiently small. Around each particle so ingested a vacuole is formed, and the fluid in this becomes increasingly acid, and at the same time digestive. Krukenberg (9), Reinke (10), and Miss Greenwood have conclusively proved these and similar food vacuoles in the amœba and other Protozoa to contain a pepsin or digestive ferment, which, as Le Dantec has shown by very delicate tests, exerts its action in an acid medium (the general protoplasm of the cell-body being alkaline); this digestive process leads to the solution of food-stuffs,

preparing them to be taken up by the protoplasm of the organism. If the foreign substances be incapable of digestion they are sooner or later extruded. It is by this formation of digestive vacuoles that the amœba acts upon and destroys bacteria, diatoms, and other microbes ingested by it. There are, however, microbic forms around which it would seem that no proper vacuolation is developed, or if developed, the acid digestive fluid is neutralised by substances discharged from the parasites; where this is the case, instead of destruction there is continuance of vitality and actual multiplication of the invading or parasitic form, leading to the eventual death of the amœba. Metchnikoff has observed this chain of events in one of the amœbæ which ingests and becomes the host of a minute rounded form, the Microsphæra. Phenomena of like nature may be observed among the ciliate and flagellate infusoria. Here it is worthy of note that bacteria, which, as we shall see, are the main causes of inflammation in higher animals, are in these lowly forms an important, if not essential, source of nutrition. So far it has not been found possible to gain pure cultures of the amœbæ: in other words, they are unable to obtain adequate nourishment from the various media of the laboratory. It has been found, however, by Frosch, Mouton, and others (11) that if certain of the commoner forms be isolated, placed in a suspension of a pure culture of the bacillus coli, or certain other species of bacteria, and then be "sown" upon the surface of a tube of sterilised agar broth, active growth and multiplication ensue, the bacilli being taken up and used as food. While these phenomena may primarily be regarded as the method employed by the Protozoa for the assimilation of food-stuffs, they also are clearly the means whereby the Protozoa defend themselves against living organisms which have gained entrance into them,

and thus form the reaction to possible injury; for when in certain cases the means of defence are overcome, the parasitic organisms gain the upper hand and lead to death.

There is yet another reaction to injurious influences exhibited by the Protozoa into which it is necessary to enter at some length. This is exhibited by the amœba, but can be and has been most fully investigated in the myxomycetes—multicellular forms which can with equal propriety be classed as animals or plants, although usually they are included among the latter. These organisms form large plasmodia (masses of protoplasm, that is), in which, under ordinary conditions, the nuclei are the only indication of the individual cells which by their fusion have formed the masses. They are to be met with in leaf mould, and on the surface of moist decaying wood, over which they creep with an amœboid movement; and inasmuch as they may attain great size—some species attaining twelve inches or more in length—they form admirable material for biological study.

Twenty years ago Stahl (12), investigating one of these myxomycetes (the *Æthalium septicum*, an organism found in tan-pits), showed that if placed upon a moistened surface close to a drop of infusion of oak-bark, the plasmodium moved actively towards and into the infusion; if placed similarly near to a solution of glucose (0·5 per cent) it moved with equal rapidity away, and so also in the case of solutions of various salts. These observations of Stahl were (if we except Engelmann's observations in 1881 upon the tendency of sundry bacteria to remove from regions poor in oxygen to those where oxygen is present in abundance) the first of a series of observations upon the attraction and repulsion of plants and portions of plants by chemical substances. To this property Pfeffer (13), who has made the fullest

series of studies upon it, has given the name of *chemiotaxis*, in place of Stahl's narrower "trophotropism"; and one speaks of a positive or a negative chemiotaxis according to the attraction or repulsion exerted. If, as Metchnikoff has pointed out, the advancing edge of one of these plasmodia (of Physarum) be injured by cauterisation, the region of injury dies; the protoplasmic currents, which had been advancing, reverse themselves abruptly, and within an hour the plasmodium has moved away, leaving the debris of the destroyed region behind. These experiments are so simple, and the results obtained seem so natural, that it may be asked whether it be worth while to attach a name to this property of living matter. Yet the name is in itself an aid to bearing these properties in mind; and, as will be pointed out later, the recognition of them is of material help in solving certain of the difficulties that present themselves in the study of inflammation in the higher animals. Among these myxomycetes another point can be made out. Stahl observed that the plasmodium of *Fuligo*, which at first moves away from a two per cent solution of common salt, will after a time (more especially if it has suffered from lack of water) adapt itself to the solution, advancing its pseudopodia or protoplasmic processes into it. With other myxomycetes the same *adaptation* has been observed. That is to say, by use or adaptation a negative may be transformed into a positive chemiotaxis. To this change I shall have occasion to revert.

A similar, and suggestive, series of adaptations has been noted by Musgrave and Clegg (14) in their studies upon amœbæ. They note that these in their natural environment—the pathogenetic forms in the large intestine, for example—are selective, feeding upon only one of the many surrounding species of bacteria. Away from that natural environment they grow abundantly

upon the surface of agar tubes in association with this one form. By the gradual addition of pure cultures of another bacillus, with which, at first, growth is not possible (the amœbæ not taking them up, and starving as a consequence), the amœbæ first become accustomed to this foreign form, then take up occasional individuals, until eventually they will feed upon and grow in a pure culture of the second form, in the total absence of members of the first species. Nay, more, these observers noted that one particular amœba, isolated from Manila tap-water, and grown in conjunction with a species of bacteria present in that water, set up abscess-formation when inoculated with it into the liver of animals of the laboratory: from such an abscess growths of the amœba could be obtained in association with the microbes in question. But if passage were made through two more animals of the same species, setting up in them liver abscesses, it was found impossible to gain growths in like manner. The amœbæ were there, but growth in the tissues had changed their habits. They had clearly accustomed themselves to a wholly different form of food —presumably to cell-products of the organism; a point which throws light upon the frequent occurrence of tropical abscesses of the liver, in which amœbæ are present without associated bacteria.

The Response to Injury among the Metazoa.— Passing from the Protozoa to the Metazoa, we reach immediately (or almost immediately) a series of beings in which the division of labour among the cells has led to the development of three cell-layers—an outer ectoderm, an inner endoderm, and an intermediate layer of mesoderm. Even in the very lowest forms among the Metazoa it is noticeable that of these three layers there is one, the mesoderm, whose cells have the especial function of reacting when any irritant or injurious stimulation is

applied to the organism. Taking what are perhaps the simplest forms in which to observe the relationship and properties of these layers, Metchnikoff has studied these results of injury in the larval forms of Astropecten and other echinoderms. At one well-recognisable stage these larvæ resemble little more than the gastrula stage of the

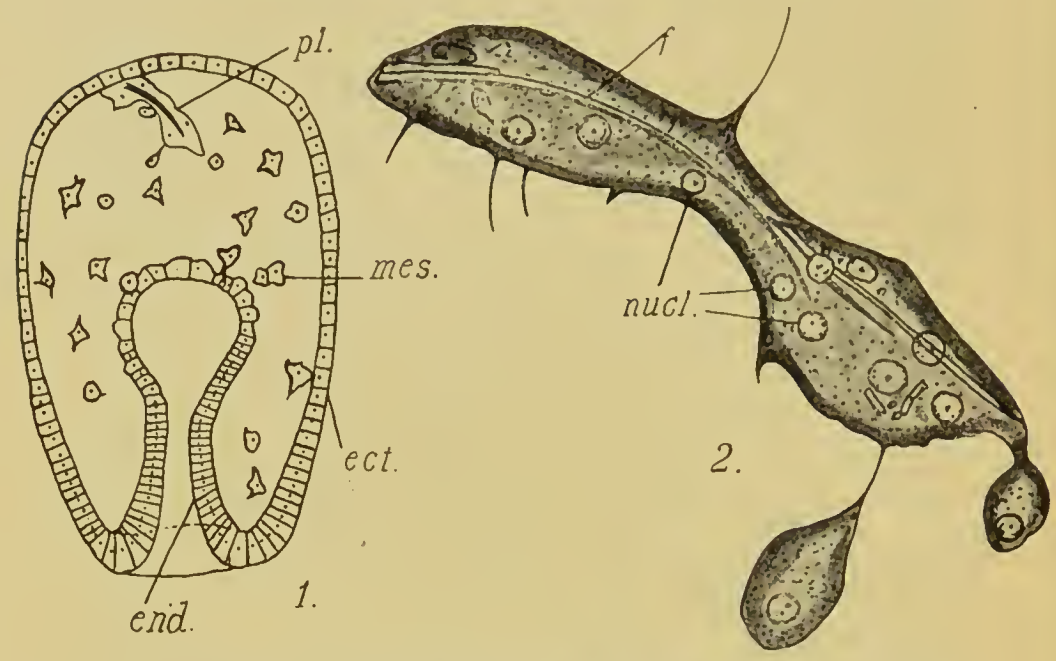

FIG. 1.—1. *Larva of Astropecten*, modified from Metchnikoff to show *end*, endoderm; *ect*, ectoderm; *mes*, mesodermal wandering cells; *pl*, plasmodium of mesodermal wandering cells formed around foreign body which has punctured the endoderm. 2. The *Plasmodium*, from the same larva, highly magnified; *nucl*, nuclei of the fused wandering cells; *f*, spicules of foreign matter around which the cells have collected.

embryologist; the endoderm or hypoblast appears as a cul-de-sac—an invagination of the ectoderm or epiblast—while the mesoderm is represented by amœboid cells, budded off from the endoderm, lying or floating in the semiliquid substance filling the general body-cavity.[1]

[1] As indicating the earliest stage of these wandering cells it is noteworthy, as MacBride (15) has pointed out, that in the gastrula of *Echinus esculentus* two forms of wandering mesenchyme cells are present in the body-cavity: one obviously stellate, and attached to other similar cells and to the body-wall by long processes; the other, rounded forms

The ectoderm is so delicate that any sharp substance can readily penetrate into the body-cavity; and, when this happens, it is noticeable that the wandering mesodermal cells make their way to the foreign body, attach themselves to it, and fuse into plasmodial masses, thus forming a wall, as it were, around the invading substance, and cutting it off from the general body system. Here, then, in an organism possessing neither nervous nor vascular system, the reaction to injury, when that injury has not been sufficiently intense to cause destruction of the outer layer of cells, is simply and solely confined to the wandering cells of the body; there is no effusion of fluid; there is not necessarily phagocytosis on the part of these cells; any digestive and destructive action on their part—any attempt in this way to remove the foreign body—must then be by excretion, *by extracellular action.* At the same time, this fusion of the cells and formation of a plasmodium around foreign substances of greater diameter than the individual mesodermal cells may be looked upon as a mechanism whereby the equivalent of intracellular digestion is gained. But, as among these low forms cases occur in which, without the formation of plasmodia, the cells perform their destructive action upon bodies of larger size than themselves we do not lack examples of what must be considered as excretory destructive powers on their part. That these cells in the echinoderms are also capable of destroying minute foreign bodies by intracellular action, that is, by phagocytosis, has been demonstrated in the larger transparent larval form known as *Bipinnaria asterigera*; on introducing bacteria under its ectoderm the mesodermal cells are seen to approach,

(amœbocytes), which, while appearing free, are connected with neighbouring cells and the body-wall by means of excessively fine threads, along which they appear to travel. The cells at first are therefore only relatively free.

and by their long pseudopodia to adhere to and ingest the still living motile bacteria, which are rapidly digested.

Besides this reaction to injury on the part of the mesodermal cells, a further response is exhibited to a remarkable degree among the lower Metazoa—I refer to the great power of *regeneration* of lost parts, of cell-proliferation leading to the reproduction of destroyed regions. This power is best seen in the classical example of the *Hydra*, which may be cut into many pieces, each one of which is capable of growing, so that in a relatively short time it becomes a fully formed individual. It is interesting to note in relation to the frequent tendency towards hyperplasia and excessive growth following upon injury in the higher animals, that among low forms, such as *Hydra* and *Cerianthus*, the same tendency is yet more strongly marked. Thus, as J. Loeb (16) points out, if an incision be made in the stem of a Hydra, a whole new oral pole, provided with tentaeles, will branch out from the region of cell-destruction. In the actinian Cerianthus the process is not quite so extensive; yet from the lower lip of the lateral incision a set of tentacles develops in all respects similar to those around the mouth.

Ascending to the Worms, we find that the protective agency devolves upon mesodermal cells suspended in the perivisceral fluid, and again forming the peritoneal endothelium. We arrive, that is to say, at a stage in which a lymphatic system may be said to be present; for the spaces in which the free corpuscles lie are strictly homologous to the lymph-containing spaces of the vertebrate organism, and these corpuscles may be regarded as lymph-corpuscles; the peritoneal endothelium corresponds with the mesodermal peritoneal endothelium of vertebrata. It is the fixed as well as the wandering cells that take part in the process.

Among the Annelids the process of reaction to injury may be well followed in the earthworm by studying the sequence of changes that occurs around the gregarines which infest the male genital organs. While these parasites are active they by their movements prevent the adhesion of the wandering cells; but so soon as they pass into the resting stage antecedent to spore-formation, the cells form a thick mass around them. The parasite on its part forms a thick cyst-wall; nevertheless, it may not unfrequently be observed that, despite this protection, the parasite changes its appearance under the action of the surrounding plasmodium, and in fact is killed. While this is happening no change could be detected by Metchnikoff in the neighbouring blood-vessels; these appear to remain completely inactive: no exudation is noticeable nor any recognisable change in volume. The nature of the injury inflicted without doubt influences the character of the reactive process. Thus causing direct injury, either by passing a thread through the body, or by cautery, Messing (17) found that in the earthworm and leech regenerative changes are both more pronounced and of more rapid development than is the accumulation of wandering cells. In six hours the injured epithelium might show definite signs of regeneration, while at this period but few mesodermal cells had collected.

While among the Worms a well-developed and closed vascular system is not infrequently present, in other animal forms, which in most respects present a much more complex and advanced development, namely, in the Molluscs, Arthropods, and Tunicates, this is not the case. In these the blood pours from the tubular heart sooner or later into the lacunæ of the general body-cavity; and whether veins and capillaries (*i.e.* finer vessels lined with endothelium) be absent (as is most usual), or present (as

in the Cephalopods), the blood is sucked back from the body-cavity into the heart. This incomplete circulation, interesting as it is in connexion with the development of the vertebrate circulation, is interesting also because its incompleteness in these large and widespread classes of animals prevents reaction to injury from being associated with vascular changes. The blood in these animals, circulating through the ramifications of the body-cavity, is evidently a mesodermal fluid, if it may be so termed. Its corpuscles are clearly mesodermal; and without going into full details as to the properties of these corpuscles, it may be said that they represent an interesting series of stages in the subdivision of labour. For example, as Hardy (18) has shown us in a low form of crustacean like *Daphnia* (the water-flea), but one form of cell is present, whereas in the highly developed *Astacus* (the crayfish), there are three distinct forms of leucocytes (no red corpuscles being present), each of which appears to have distinct functions. The one form in Daphnia has the property of taking up fat globules and food particles from the alimentary tract, foreign particles, such as granules of carmine or Indian ink, and the spores of parasites (*Monospora*, Metchnikoff); it is granulated, containing minute spherules which stain with basic aniline dyes (basophil granules), and in certain circumstances it may be seen to explode with lightning-like rapidity. In the higher Astacus there are in the circulating hæmal fluid two varieties of cells: one is extraordinarily explosive; when removed from the body-cavity it gives off fine blebs or vesicles of its substance with such rapidity that, unless the greatest care be taken, nothing is seen of the cell save its nucleus; this form is phagocytic: the other form is far more stable, and is loaded with large spherules which have a great affinity for acid dyes—they are eosinophilous—may be actively

extruded, and undergo decomposition; these cells never act as phagocytes. The third form, with basophil granules, is rarely found in the blood, and then only as the result of special stimuli; but it is present in considerable numbers in the peculiar tissue which forms a sheath around certain of the arteries—Haeckel's "Zellgewebe"; this form is phagocytic, and can be seen to contain globules of ingested fat.

Metchnikoff (19) demonstrated, in his most remarkable study upon a disease of Daphnia caused by the entry of the spores of a yeast-like organism (the Monospora) into its body-cavity, that its one form of leucocyte can be seen to react swiftly towards the spores; the cells approach them, form a plasmodium around, and eventually digest and destroy them. If, on the other hand, in consequence of their great numbers or the relative paucity of the leucocytes, certain of the spores be not attacked and develop uninterruptedly into mature torulæ, the leucocytes show no tendency to approach them—in fact, their neighbourhood leads to the explosion of the leucocytes—and the torulæ, multiplying, lead to the death of the organism. Often, again, brown eschars may be recognised upon the transparent carapace of a Daphnia, due to injuries by other individuals; beneath these scars are to be found masses of leucocytes which remain in the region of injury until the cells of the tissue have proliferated, and there is complete union and repair.

In addition, then, to the immediate reparative and protective reaction of the leucocytes, there is exhibited among the higher invertebrata a later reaction in the shape of proliferation of the fixed cells; nay, at times the proliferative and regenerative process may be the more pronounced. This proliferation can be very great; and cells of all forms, whether of hypo-, meso-, or

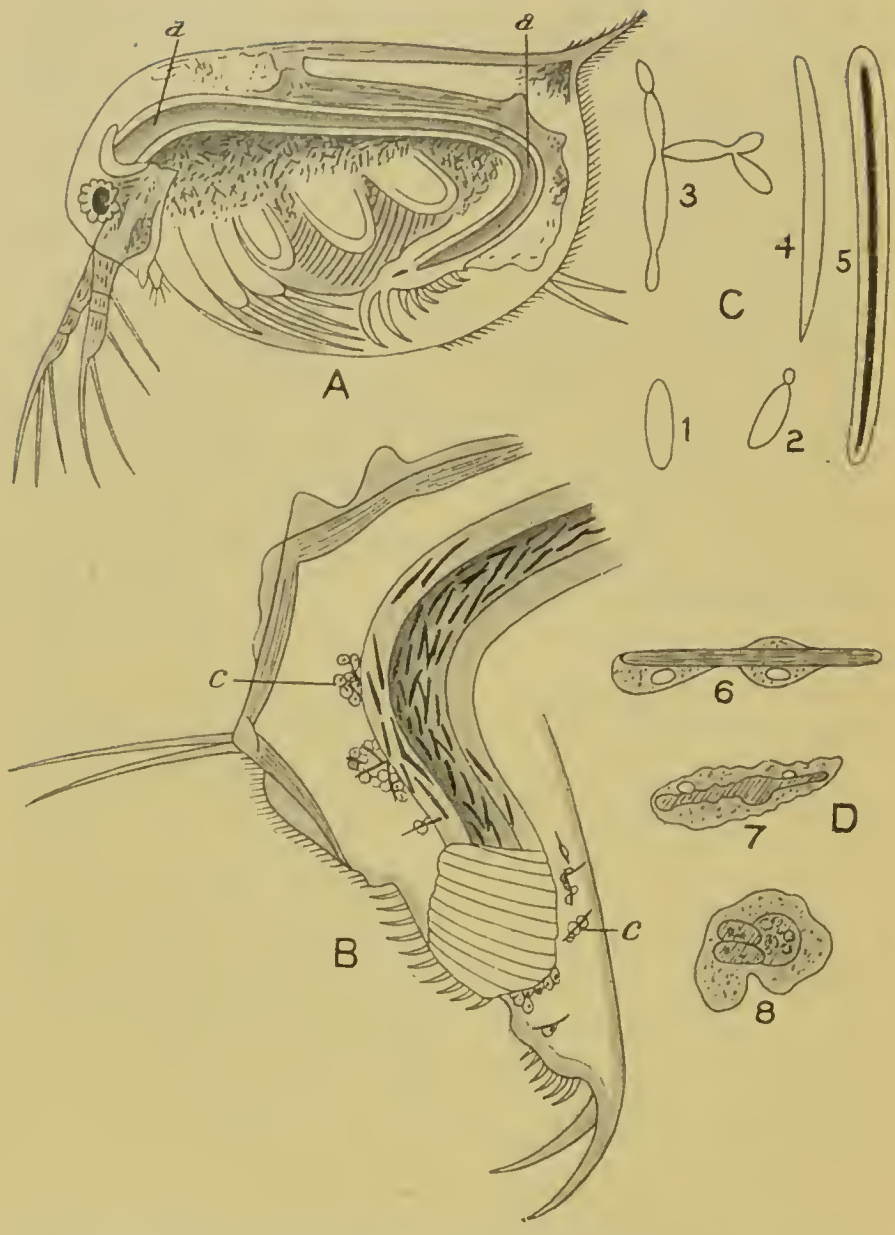

FIG. 2.—*A*, A *Daphnia* (water-flea) invaded by the parasitic yeast, *Monospora*. The deep shading, more particularly below the intestinal canal (*a*), is due to the mass of spores which have penetrated into the body-cavity. *B*, Anal end of an infected Daphnia. The elongated spores are to be seen in the lumen of the gut (*b*), in the walls of the same, and others which have penetrated the walls and have entered the body-cavity are seen with leucocytes attached (*c*, *c*). *C*, Stages in the development of Monospora: 1, Individual elongate oval torula; 2, a torula budding; 3, do., later stage; 4, much elongated torula prior to spore-formation; 5, torula with contained spore. *D*, Stages in the destruction of the spores: 6, spore with two leucocytes attached; 7, 8, later stages of erosion and digestion. —METCHNIKOFF.

epiblastic origin, and tissues so highly developed as the muscular and nervous, may participate in it. In illustration of the ample power of tissue-reproduction after injury possessed by these animals, I need but mention the trite examples of the reproduction of the hinder segments of divided worms, and in crustaceans the restoration of injured and cast-off claws and appendages.

Many more instances might be given to show that the reaction to injury remains essentially a reaction on the part of the wandering and fixed mesoblastic cells of the organism, followed in sundry cases by proliferation of the fixed epi-, meso-, and hypoblastic cells, and by repair where these have been destroyed. Although these arthropods, molluscs, and tunicates have a vascular system, yet, since this is open, changes in it, did they occur, could scarcely modify the inflammatory process.

The Response to Injury among the Vertebrata.— If now we pass to the vertebrates, the picture presented is far more complex; not only do these present a highly developed nervous system, but the blood is enclosed in a complete vascular system. It is but just to call attention again to the fact that many authorities deny that up to this point we are justified in speaking of inflammation, urging that inflammation can only be said to be present when there is "flaming," *i.e.* increased redness and heat, due to increased blood-supply, that is to say, to vascular changes. While this position is etymologically correct we cannot accept it, because, as will be pointed out in the next chapter but one, we find that where this "flaming" is present, the process, nevertheless, in essence, is identical with that in the lower animals devoid of a complete vascular system.

CHAPTER III

THE EXPERIMENTAL PRODUCTION OF INFLAMMATION IN NON-VASCULAR AREAS

Let us begin with the succession of changes that occurs in the simplest case, namely, *in a non-vascular area, in one of the lowest vertebrate forms*—for instance, in the embryonic Axolotl ten to fifteen days old; let us curarise it, and apply a minute crystal of silver nitrate to the side of its flattened transparent tail-fin, washing away the remains of the crystal with salt solution; or again, we may pass into the tail a small needle filled with finely powdered carmine. By either procedure a certain number of cells is destroyed. The neighbourhood of the injury now becomes swollen, and the surrounding cells tumefied, vacuolated, and less refractile. This is the *first stage*—that of injury and modification of the surrounding tissue. In a little time a few wandering cells (leucocytes) approach the injured region; by the next day these are present in fair numbers, and can be seen to have taken up the particles of carmine or debris of the destroyed tissue. This is the *second stage*—that of immigration of leucocytes. There are no vessels in the transparent fin of these young axolotls, no dilatation of those nearest to the fin, and no diapedesis. All the leucocytes that pass to the part are pre-existing wandering cells of the connective tissue,—a point of some little

importanee in eonnexion with the origin of eertain of the pus-eells in the suppurative proeess of higher animals. The *third stage* is that of repair, of proliferation of the injured epithelium, return of the fixed eells of the tissue to their previous state, and emigration of the wandering eells.

A very similar progress of events oceurs if the experiment be repeated upon the tail-fin of the young Newt. The same rapid alteration in the large branehed eonneetive-tissue eells (which beeome vaeuolated as their long proeesses are drawn in and shortened), and the same immigration of motile cells from the surrounding eonneetive tissue are to be seen; but here we now find the earliest evidenee of vaseular partieipation, for, aeeording to Metchnikoff, eomplete arrest of the eirculation may oceur in the nearest vaseular loop. By the next day the parts have returned to the normal eondition.

If from these eases we pass to mild inflammatory disturbanees affeeting the non-vascular regions of animals far higher in the scale, we again diseover a like proeess of events. For this purpose *the cornea* affords the tissue of eleetion; in health it is absolutely non-vascular, perfectly transparent, and so thin that it ean readily be examined mieroseopically. The eornea of mammalia, and indeed of vertebrates in general, is formed of fibres which run in layers parallel to the surfaee. These fibres, while roughly arranged side by side and parallel to one another in any given layer, are plaeed at an angle to the fibres of the layers above and below. Although free from blood-vessels the cornea is far from being devoid of ehannels along whieh lymph freely passes. Between the several layers there exist spaees in which lie the flattened eonneetive-tissue eells of the organ; and, by means of numerous fine channels, these spaees around the eells are eonneeted with similar

spaces lying in front, behind, and at the sides. Through this rich anastomosis of channels there is a free flow of lymph. These channels are really continuations of the body-cavity of the animal; they represent, and in fact play the same part as the single body-cavity of such a simple form as the larva of Astropecten, while the cells lying in the spaces are mesoblastic cells which have become fixed.

Few studies are better calculated to impress the investigator with a sense of the depth of the well at the bottom of which truth lies, than a research into the abundant literature dealing with observations upon the stages of the inflammatory process as it occurs in the cornea, and with the deductions therefrom. The adherents to successive forms of inflammatory belief have found in experiments upon this simple tissue ample support for their particular creeds. Selecting from the many observations those which have stood the test of time, I will begin with the simplest, and pass on to those dealing with an increasing intensity of the inflammatory process.

(i.) If, as Senftleben (20) first pointed out, the centre of the cornea of a rabbit be washed with a strong solution of zinc chloride, then, in favourable cases, although the epithelial covering be gravely injured, there may be no actual rupture of the outer layers of the tissue. Such a cornea removed twenty-four hours later may show no sign of migration of leucocytes—no sign, again, of congestion of the vessels at the periphery. The only indications of injury and reaction may be the destruction of the corneal corpuscles immediately beneath the cauterised area, and the appearance of a zone surrounding this in which the corneal corpuscles appear enlarged, distinct, and tumefied. The process may continue and advance insensibly to repair without the

intervention of leucocytes; the hypertrophying cells of the "granular" zone eventually undergoing karyokinesis, and thus by multiplication replacing the corpuscles destroyed. Here, then, *necrosis and new growth of the fixed cells of the tissue are the only recognisable factors in the process of repair of injury.* It must be confessed that the conditions permitting this simplest form of reaction are of rare occurrence; it is worthy of attention that they can exist.

(ii.) By a slight modification of the preceding conditions another factor may be brought into play. If, after cauterisation in the manner above described, a break be made into the cauterised surface; or if, again, without cauterisation, a little of the corneal tissue be removed, then in a few hours a small whitish opacity is to be noticed within the corneal tissue in the immediate neighbourhood of the break in the continuity, and upon examination this opacity is found to be due to a massing of small round cells. As there is at this moment no sign of proliferation of the connective-tissue cells of the cornea, these newly collected cells can only be leucocytes; and further examination of their properties proves them to be such: there is, however, no evidence of dilatation of the peripheral vessels, no indication of diapedesis through their walls. The leucocytes, therefore, can only have entered into the wound from the cornea itself and from the conjunctiva and the lacrimal fluid bathing it.[1] In this experiment the inflammatory process is represented by destruction of tissue and immigration of leucocytes, followed by repair; neither the vascular nor the nervous system play any part in it. We are forced to the conclusion that the leucocytes have massed them-

[1] It is to be noted that the lacrimal fluid contains, even in perfect health, occasional leucocytes which have found their way into it through the tissues.

selves in the injured area purely on their own initiative; and that there must be an attraction, a chemiotaxis or chemiotropism, leading them actively to approach the region of cell-destruction.

(iii.) Or we may proceed a step further. A fairly severe aseptic injury can be produced by cauterising the centre of the cornea. In thus treating the pigeon's cornea Goecke (21) noted that the wandering of cells towards the damaged area is first visible twelve hours after the injury, and then proceeds from the periphery. Obviously the wandering cells are white blood-corpuscles, and pass from the peripheral vessels. In twenty-four hours the process and the accumulation of round cells reach their climax. Some of the new-comers break up, others, according to Goecke, show signs of division. But soon these foreign cells commence to wander away, and at the end of thirty-six hours scarce any are left.

Turning to the fixed cells of the part, it is deserving of note that, before ever a leucocyte has reached the injured area, the corneal corpuscles, bordering upon the area of cauterisation, show evident signs of enlargement and growth. On the second day there are indications of active proliferation; and these newly formed corneal corpuscles behave exactly like certain white blood-corpuscles, from which they are indistinguishable. The vexed question of the relative part played by the wandering white corpuscles of the blood and wandering young connective-tissue cells will be touched upon later. It is, however, well to impress upon the reader that, at a certain stage, what we may term histogenous and hæmatogenous wandering cells are wholly indistinguishable by our present methods of study. The fight has been particularly bitter regarding these cells in connexion with this very subject of experimental keratitis.

(iv.) The observations made upon these three more

simple cases help us materially to understand the series of events which occur in more intense inflammation of the cornea, such as that produced by injuring the surface and causing the entrance into the injured region of a small quantity of a pure culture of the pyococcus aureus. This may be accomplished by injecting the culture into the centre of the healthy cornea by means of the needle of a Pravaz syringe (Jacobs) (22). The micrococci so introduced grow rapidly, the growth so extending along the lymph-spaces that a branched mass of the microbes is produced, having the spot of inoculation as centre. Around the growth as it extends may be seen a sharply marked area in which the corneal corpuscles show evidences of degeneration; the nuclei stain faintly, and the corpuscles, speaking generally, have a shrunken appearance. Here, again, the first effect of a microbic, as of a simple chemical injury, is to bring about degeneration of the fixed cells of the tissue. Within eighteen hours the zone of proliferating cocci and cell-degeneration is well marked; and now the second stage begins to be clearly manifest, namely, the determination of leucocytes to the seat of injury. Within twenty-four hours there is a dense packing of these corpuscles around the central degenerated area, and great numbers of leucocytes may be seen converging along the lymph-spaces from the periphery of the cornea. This is the second stage of the process, the first stage of obvious reaction to the injury inflicted by the invading micro-organisms. If, as by Cohnheim[1] (23) in his original experiments upon the injury to the cornea, more careful examination be made into the stages of the determination of leucocytes, it can be seen that this determination is closely related to

[1] There can be no question that Cohnheim in his experiments induced not a simple keratitis but one which in the absence of aseptic precautions rapidly became infective and suppurative.

changes set up in the veins at the periphery of the cornea; they become more prominent, the region has a congested appearance, the smaller as well as the larger vessels are dilated, and there is abundant evidence that the leucocytes are passing out from the contained blood into the surrounding lymph-spaces. Indeed the accumulation of leucocytes shows itself first at the periphery of the cornea near the vessels, and gradually approaches the region of injury. Into the mechanism of this diapedesis, and into a fuller description of the changes that take place in the blood-current in these distended vessels, I shall enter later when discussing the changes in highly vascular regions. Suffice it to say here that no distinction can be made out between the behaviour of the leucocytes in the previous experiment, when they entered the wounded area from the external surface, and in this where the majority find their entrance from the blood; as in the previous case the part played was evidently active, so must it be here also. We cannot arrive at any other conclusion than that some attractive force leads to their determination towards the inflammatory focus. It is the polymorphonuclear leucocytes which at first most actively migrate. As Councilman (24) points out, in experimental pyococcic inflammation, as early as fifteen minutes after inoculation of the centre of the cornea a greater number than usual is seen in the conjunctiva. A more granular, more sluggishly amœboid form follows, most numerous in eighteen to twenty-four hours, while lymphocytes are not visible until the fourth day, and then do not so much pass out of the vessels as from the sheath of lymphoid tissue surrounding them. As we can easily show, by repeating the experiment, many of these leucocytes take up and contain numerous cocci, while other cocci remain free in the tissue-spaces. Many of the leucocytes degenerate and present a broken-down

appearance; and, as at the same time an increasing area of the corneal tissue becomes disintegrated, an *ulcer* appears. According to the virulence of the culture and the reaction on the part of the organism, the process may now extend, a larger and larger portion of the corneal tissue becoming affected; or, on the other hand, there may

FIG. 3.—Mild grade of keratitis, commencing regeneration after forty-eight hours. 1. Peripheral zone of corneal corpuscles, showing enlargement with nuclear multiplication. 2. Zone of degenerating granular corneal cells (*b*). 3. More central area of cells (*c*) destroyed and broken up by the action of the caustic. *a*, Processes from proliferating corneal cells, with nuclei, advancing into region of irritation and degeneration.—After SENFTLEBEN.

be an arrest of the progress, the massing of the leucocytes preventing, as a barrier, the further extension of the micrococci into the lymph-spaces;[1] while at the same time there is an advance of newly formed capillary vessels into the previously non-vascular tissue. It is to be noticed that the blood-vessels at the periphery of the cornea are

[1] Into the details of this action I shall enter more fully later.

prominent and dilated, and from them fine new vessels with very delicate walls pass towards the injured region. At the same time many of the corneal corpuscles, outside the area of destruction, can by appropriate staining be seen undergoing mitosis and proliferating. Thus the active repair of the tissue is initiated. The regenerative process is best observed in young animals by the use of caustics without causing a break in the continuity of the surface. Twelve hours after injury indications of cell-growth may be made out; in twenty-four hours mitoses are numerous, but occur only in the zone immediately surrounding the necrosed area. The corneal corpuscles become larger, their protoplasm more abundant; the cell-bodies stain more deeply; the nuclei become more rounded and also more deeply stained; the cells give off long processes—always towards, never away from, the necrosed area—and with division of the nuclei the young nuclei make their way into the processes, and so into the dead tissue. In this way new typical corpuscles are formed in the course of the branches, which further show abundant cell-inclusions; in other words, the growing tissue-cells feed upon the migrated leucocytes.

CHAPTER IV

THE EXPERIMENTAL PRODUCTION OF INFLAMMATION IN VASCULAR AREAS

From this study of inflammation, as it occurs in a region primarily devoid of blood-vessels, let us now pass on to the more complicated process of inflammation in vascular areas; and, as in the previous case we considered an ascending or advancing series of reactive changes, so here let us begin with the slightest injury associated with the mildest reaction, and pass onward to states in which the inflammatory manifestations are more and more pronounced.

(i.) If an incision be made with a perfectly aseptic instrument into the skin, also rendered aseptic, and be so made as to divide the dermis and tissues immediately below, without at the same time injuring any large vessel, it is the common experience of modern surgeons that repair takes place with the minimal amount of change recognisable as inflammatory. Repair takes place indeed so rapidly that, if the divided structures have come or have been brought into immediate contact, there may be firm adhesion at the end of twenty-four hours. This is *primary union*, or union by first intention, which, rare in the old days, commonly occurs in this era of aseptic surgery. The full sequence of events in these cases cannot, it is true, be well determined by continuous

microscopic examination; but if the rabbit or dog be employed, and tissues, wounded in the manner described, be removed and examined at successive short intervals, we see that the changes which occur are mainly, nay, almost entirely, related to the pre-existing cells of the part. The section divides a certain number of capillaries; but in the very act of division the divided walls are apparently brought together; and, partly by this means, partly by contraction, the lumina of these minute vessels become occluded, and the hæmorrhage into the wound is altogether inconsiderable. Within an hour after the operation it is evident to the naked eye of a careful observer that the immediate neighbourhood of the wound is reddened and tumefied, but only slightly; and, associated with this, there is a feeble exudation between the opposed surfaces. But the exudation is not great, and even within this first hour after the infliction of the wound there may be development of fibrin and coagulation of the exudate, leading to a provisional cicatrix cementing together the opposed surfaces. In this exudation, and in the tissues in the immediate neighbourhood, the leucocytes that have undergone diapedesis may be few and far between, and may scarcely attract attention. The reaction, then, on the part of the vessels and of the leucocytes is of the slightest. At times the dilatation of the vessels is more considerable, and with this there is a fair amount of oozing into the wound of a thin serum, which has little tendency to coagulate. Thus it has not been an infrequent experience of surgeons that if an extensive skin-flap be sewn up completely the amount of serum accumulating between the surfaces of the wound during the next few hours causes not a little tension and discomfort. If one or two of the stitches are cut and this serum allowed to drain away the parts unite forthwith. It has become the practice to make allowance for this serous

oozing by not completely closing one end of such a wound, and inserting there temporarily a "drain" of sterilised gauze, so that this fluid escapes immediately and primary union is facilitated.

Study of sections in these cases shows that the main part is played by the pre-existing cells of the part; of these a certain number (not so many as might *à priori* be expected) are destroyed immediately, and show all the signs of disintegration; a number relatively large have been injured only, their nuclei remaining intact, though their processes or some portions of the cell-bodies have been cut through. It is difficult to determine these injuries in the small cells of the cutaneous tissues; they are better seen in the peritoneum when slight inflammatory changes have there been induced. It can, however, be made out that the cells in the immediate neighbourhood of the wound became enlarged, and, without showing signs of division, prolong themselves (that is to say, send out prolongations) into the region of the provisional fibrinous cicatrix. In this way, before the end of the second day, there may be a more or less complete replacement of the primary unorganised cementing substance by organised growing tissue,—formed, in the first place, by the interlacing of processes from the neighbouring cells; in the second, and later, by a multiplication of these cells, together with a development of new capillaries, few in number, which branch off from the slightly congested vessels in the neighbourhood. Thus in this case the process of repair is characteristically associated with hypertrophy and the new growth of the fixed cells of the tissue; while vascular changes, exudation, and leucocytosis are relatively little marked. I have, however, never come across a case in which they have been entirely absent, save when the section has been truly extravascular—that is to say, when it has not penetrated into

the vascular region of the skin, and has affected only the epidermis and outermost layers of the dermis. In such cases the response to injury may show itself purely as a proliferation of the epithelial cells. As I have said, observations of this nature labour under the disadvantage that they must of necessity be discontinuous. I bring them in at this point, inasmuch as they represent the mildest condition of the inflammatory reaction. I have not personally observed this series of changes in tissues which permit of continued study under aseptic conditions; neither am I acquainted with any observations wholly fulfilling these conditions—made, that is to say, upon transparent vascular tissues subjected to the mildest aseptic injury and examined continuously under the microscope.

(ii.) The response to injury in the cases just mentioned was of the slightest. Let us now pass on to cases in which it becomes more pronounced; and in order to continue the comparative study of inflammation I would first describe the series of *events in a highly vascular and transparent region* in a low vertebrate animal, namely, in the tadpole's tail. If this be injured, either by the application of a caustic or by the introduction of a foreign inert body into its substance, a definite advance upon what was recognisable in the case of the axolotl, for example, is to be made out. Here the tail is very vascular, the wandering cells in the connective tissue are very few in number, while the blood is fairly rich in leucocytes, which are small relatively to the size of the vessels. The results of injury are a congestion of the vessels, noticeable within fifteen minutes, and a well-marked determination of leucocytes to the injured region. These cells, in the main, pass out from the vessels; the few leucocytes pre-existing in the tissue appear to play a very small part. Compared with the axolotl experiment

this observation is of considerable interest. *Instead of a slight reaction slowly developing there is a rapid reaction*; instead of a slight accumulation of leucocytes there is a most pronounced accumulation. If there be any meaning in the determination of leucocytes to the region of injury, then evidently the active participation of the vessels of that region in the reactive process is fraught with benefit —it is a further important factor developed with the development and advance of the organism.

The fuller details of this vascular interference in the inflammatory process have been followed by many observers, among whom first and foremost was Cohnheim (23), and to this end the frog has supplied the most convenient means in regions at once vascular and fairly transparent, such as the web of the hind feet, the tongue, and the mesentery. Other observers passing higher in the scale of vertebrates have employed the mesentery of the cat, dog, and other mammalia. Suffice it to say that, with slight modifications due to local conditions in the tissue examined rather than to the animal selected, the process has been found to present the same features throughout the whole of the adult vertebrata, from the reptilia upwards. For general examination, perhaps, the best and simplest method of observing the succession of changes that follow injury of a vascular area is to be found in Coats' modification of Cohnheim's original experiment upon the frog's web (25). In order to reproduce as nearly as possible the conditions of an early wound, instead of employing a caustic or chemical irritant, a small portion of the cutaneous surface is nipped off—the section being just deep enough to pass through the cutaneous layers without causing hæmorrhage. For the experiment to proceed satisfactorily, it is necessary that the frog be curarised after having been pithed. The web of a small frog is so thin that the changes occurring

in and around the vessels of the part can readily be followed even with a high power of the microscope.

The first change noticeable in the immediate neighbourhood of the injured membrane is a dilatation of the vessels, first of the arteries and then of the veins; and in this first phase there is a very evident acceleration of the blood-flow. At this early period the capillaries show little evidence of dilatation, but in the course of an hour expansion is readily distinguishable, and sundry capillary channels, previously invisible, become occupied by blood and show themselves. This first stage lasts for an hour, or in some cases perhaps two, and is followed by a phase of slowing of the blood-current. While previously a well-marked axial stream of corpuscles had been evident, with a peripheral zone of plasma devoid of corpuscles, the former now broadens out, the latter becomes less and less, and as it narrows increasing numbers of the clearer rounded hæmal leucocytes are to be seen in it travelling at a slower rate than the more axial stream, and every now and then stopping beside the walls of the vessels, and after a short stoppage passing on again. The leucocytes conduct themselves as if they have become "sticky."[1] We see the first signs of *margination.*

As the current becomes yet slower all distinction between axial and peripheral streams is lost; the corpuscles, closely packed together, fill the whole lumen; the leucocytes in increasing number approach the vessel-walls; they adhere more firmly, and so long as a current is recognisable the action of the stream leads them to

[1] Even so low down in the scale as Daphnia this same peculiarity is noticeable: there in health, as Mr. Hardy (18) has pointed out, the leucocytes move freely; but, if the slightest injury be inflicted upon the carapace, the leucocytes, previously unadhesive, soon show the tendency to adhere to the walls of the body-cavity beneath the region of injury and elsewhere.

assume a pear-shaped appearance, the rounded ends pointing in the direction of the current.

As the stream slows gradually the corpuscles may at last move in a series of jerks synchronous with the beats of the heart; or frequently in the veins and capillaries

FIG. 4.—Inflamed mysentery of frog to show margination of leucocytes in the dilated capillaries (*a*); migration of leucocytes (*b*); escape of red corpuscles (*c*); accumulation of leucocytes outside the capillaries (*d*).—After RIBBERT.

the mass of blood may be seen moving slowly first in one direction, then in the other. Frequently one or other of these stages is followed by complete stagnation, or *stasis*, of the blood in the vessels of the injured area —I say frequently, for at other times little or no absolute arrest is seen in the vessels. Accompanying this stage, although observers employing other and chemical methods of inflicting injury have in general

omitted to call attention to the fact, there is already a considerable oozing or exudation of clear fluid from the wound; there is, that is to say, an outpouring of lymph, and this apparently from the distended vessels. Now, with the slowing of the stream the leucocytes, accumulated next to the walls of the small veins and within the capillaries, pass from the interior to the exterior of these vessels; and, if the process be studied carefully with a higher power, it can be seen that this mode of passage is of an active, or apparently active nature.[1] A series of leucocytes can be distinguished, some of which are rounded or flattened, in immediate contact with the wall of the vein; others possess a prolongation passing into the wall; in others, again (or in the former if they be watched in the fresh specimen), the prolongation enlarges on the outer side of the small vessel while the portion of the leucocyte within the vessel becomes smaller. The final phase of this act of migration is that the whole leucocyte passes through, and is found in the lymph-spaces around the vessel-wall. This process of migration may be so general that in the course of five or six hours all the small veins of the region show a crowd of leucocytes situated along their outer surface. With these a greater or smaller number of red corpuscles may also make their escape.

In this modification of Cohnheim's experiment a further stage is to be recognised. While at first the fluid exuded was clear and relatively free from cells and cell-debris, now, as the inflammatory process continues, an increasing number of leucocytes is contained in the exudation. The leucocytes do not remain in the immediate neighbourhood of the vessels, but many of them pass

[1] The process can be fully made out if at this stage the wounded region be removed, fixed immediately in weak osmic acid, and prepared for examination by the higher powers of the microscope.

on to the injured surface; still, it would seem, by active amœboid movement. Thus at the end of six hours this surface may be covered by a serum or fluid containing large numbers of these leucocytes. Here then we have the first step towards the formation of a scab or provisional protective covering to the wound.

Further observations cannot well be carried out in the pithed and curarised frog; but if an unpithed, non-curarised animal be taken, and the observations upon the earlier stage be neglected, it can be made out that if irritant matter do not find entry into the wound the process may be arrested at this point; the leucocytes upon the surface may break down, and with their breaking down and the formation of fibrin a soft scab be formed: the stasis of the blood in the distended vessels may be followed by a re-establishment of the current and slow return of the vessels to their former calibre, while beneath the thin, soft scab the epithelial cells rapidly proliferate. Within twenty-four hours there may be abundant evidence of this new growth of the epithelium tending to encroach upon and cover the wound; and not merely of new growth, but also of displacement and movements of the healthy cells at the edge of the skin wound towards and over the bared surface. At the same time the region becomes less and less populated with leucocytes, so that—not to enter fully at this point into the reparative process—within sixty hours the region may show little sign of the injury and consequent inflammation.

(iii.) On the other hand, if irritants of a microbic nature enter the wound the process may extend, as in inflammation of the cornea. More especially if the water in which the frog is kept become foul, there is a tendency in the inflammatory processes to spread, and in the cells, both fixed and migrated, of the central area to

break down, leading to the formation of a spreading ulcer. The steps of this sequence of affairs it is difficult to follow by continuous microscopic examination, partly on account of the increased opacity of the region, partly because the process extends over days rather than hours. Here, therefore, I merely mention this possible extension of the change with its main naked-eye appearances.

It is not possible by continuous observation to make out the steps of this more extensive inflammation characterised by excessive emigration of leucocytes and destruction of these together with the fixed cells of the tissue—the pyogenetic inflammation. Several observers, however, have followed its successive stages by means of examination of affected tissues at successive intervals after the infliction of injury.

CHAPTER V

THE EXPERIMENTAL PRODUCTION OF SUPPURATIVE INFLAMMATION

While, as shown by Councilman (26), Grawitz and de Barry (27), Steinhaus, Leber, and others (28), a suppurative inflammation may under certain conditions be brought about experimentally by the action of chemical irritants, such as mercury and turpentine; yet under ordinary pathogenetic conditions suppuration is induced by the growth of micro-organisms within the tissues. Hence it is better to study the conditions as induced by the inoculation of pus-producing microbes into one or other tissue. A very full series of observations upon the development of *abscesses* through the agency of the Staphylococcus pyogenes aureus has been made by Hohnfeldt (29). He inoculated small quantities of pure cultures of the microbe subcutaneously into rabbits. *Four hours* after inoculation the vessels of the region were found densely filled with corpuscles, and in them a commencing margination of the white corpuscles was discernible. Leucocytes were present within the tissue in numbers greater than normal; although, compared with later stages, they were infrequent. They were of two kinds—the mononuclear in the majority, the polymorphonuclear[1] in lesser numbers; both forms were

[1] This term while precise is painfully sesquipedalian. For myself I am willing to see it replaced by the earlier *polynuclear*, provided it be kept in mind that so used *polynuclear* is an abbreviation and not the synonym for *multinuclear*.

congregated mainly around the line of entrance of the injecting needle. Many of the connective-tissue cells were so swollen as to be rounded rather than flattened. The injected cocci, lying in the lymph-spaces, were scattered through the tissue; in part free, in part already ingested by cells, not only by the leucocytes, but also by connective-tissue cells, the number within leucocytes being not inconsiderable. Preparations made at the end of *ten hours* showed the same conditions, but more distinctly. There was ample evidence of migration of the leucocytes, margination in the congested vessels, various stages of passage through the vascular walls, and large collections of the cells in the perivascular lymph-spaces; from these they spread into the spaces between the bundles of connective-tissue fibrils. The cocci lay in the lymph-spaces in increased numbers, and the massing of leucocytes corresponded in position to the accumulation of microbes. In these regions the leucocytes were mainly polymorphonuclear, but in the boundary zone away from the cocci the mononuclear form predominated. At the end of *twenty hours* there was further accentuation of these conditions. As yet an abscess proper had not formed, but there were enormous numbers of leucocytes and also of micrococci; the fibrillæ of connective tissue were widely separated by the collections of leucocytes, which clustered round and hid the connective-tissue cells. With the completion of *forty-eight hours* a well-defined abscess had formed, separated sharply from the surrounding healthy tissue. The centre of the abscess was seen to consist of densely-packed leucocytes mingled with large growths of cocci. These leucocytes were almost entirely polymorphonuclear; and in this central area the nuclei of some showed fragmentation.[1] Neither leucocytes nor connective-

[1] Such accumulations of living and dead leucocytes in fluid matrix constitute *pus*.

tissue cells showed the slightest indication of mitosis. In the central area all traces of the previous capillaries had disappeared; in the peripheral zone they were easily recognisable, being fully injected and showing a marginal disposition of their leucocytes, many of which could be seen (in osmic acid preparations) fixed in the process of migration. The majority of the cocci lay in these leucocytes. Even where the colonies of the microbes were thickest there the majority were intracellular. Passing towards the periphery the number of cocci became smaller and smaller. At the periphery they could be seen not only to be intracellular, but also free in the lymph-spaces; and Hohnfeldt, with other observers, saw them definitely grouped within the endothelial cells of the peripheral vessels. Thus it may be noted that at this stage *the proliferating microbes extended into the healthy tissues outside the abscess.* In the centre of the abscess the original tissue had wholly disappeared; nearer the periphery light streaks and bundles of the disintegrating fibrillæ could be recognised between the leucocytes. Not till about the *tenth day* did new growth of tissue begin to show itself. During the preceding six days there had been more breaking down of the polymorphonuclear cells, characterised by fragmentation of the nuclei and by fatty degeneration of the cell-substance. But by the tenth day the periphery had begun to assume the appearance of *granulation tissue*; it contained numerous capillaries and new-formed connective tissue with characteristic epithelioid cells or fibroblasts possessing large, oval, pale-staining nuclei. In these cells, as in the connective-tissue cells of the surrounding healthy tissue, the numerous steps of indirect cell-division could be made out. *In this granulation tissue cocci were absent* and leucocytes were infrequent. In the soft, cheesy, central area masses of

cocci were still present. Whether these were living or dead Hohnfeldt did not determine; he inferred (what has since been proved by several observers to be an unsafe inference) that inasmuch as they stained well with aniline dyes they were alive.

Thus, to sum up Hohnfeldt's observations, the processes occurring in a suppurative inflammation that ends in healing are the following:—

1. Primary multiplication of the pyogenetic organisms with no immediate reaction.

2. Congestion of the region of invasion, with margination of the leucocytes; signs of degenerative changes in the tissue cells of the region.

3. Collection, in the region, of mononuclear leucocytes; then immigration of polymorphonuclear leucocytes: multiplication of the cocci.

4. Ingestion of large numbers of the microbes by the polymorphonuclear leucocytes and other cells, including the endothelial cells of the vessel-walls.

5. Increasing immigration of leucocytes until the tissue becomes densely packed. This is accompanied by a yet greater proliferation of the microbes, which extend (*i.e.* are carried by lymph-streams or by cells) into the region outside the developing abscess.

6. Coincident destruction of the tissue of the affected part.

7. Degeneration of the leucocytes within what is now the sharply defined abscess.

8. Eventual proliferation of the connective tissue at the periphery of the abscess; formation of fibroblasts in the highly vascular surrounding zone; absorption, cicatrisation, and encapsulation of the debris of the leucocytes and micrococci.

There are not a few points in connexion with these observations of Hohnfeldt that deserve discussion; very

possibly he has misinterpreted certain of the appearances. On the whole, however, he draws a full and accurate picture of the successive stages of suppurative inflammation, and I may defer discussion to a later review of the action of the leucocytes and of the formation of fibrous tissue respectively.

However, before leaving this general description of the series of anatomical changes induced by injury, there is another phase of the inflammatory process set up by pathogenetic micro-organisms which must not be passed over—I refer to those cases in which, instead of ending in repair, there is *extension and generalised disease*. The stages preceding extension vary with the nature of the microbe; thus, in some cases, the reaction to the invasion of the microbe is mainly leucocytic (as with inoculations of the micrococci of suppuration), in others it is mainly exudative or serous, the congestion of the vessels being followed by abundant exudation of serum into the tissues. This is the case in inoculation of animals—such as rabbits, guinea-pigs, and fowls—with cultures of micro-organisms which are peculiarly virulent in their behaviour towards these animals. Such a serous or exudative inflammation is, for instance, well seen if the vibrio Metchnikovi be inoculated into the pectoral muscles of a fowl. Within twelve hours, it may be, the seat of inoculation becomes greatly swollen, and on section is found reddened and congested; while from it drains an abundance of relatively clear, faintly reddish serum containing but few leucocytes.

In such a case as this the micro-organisms appear to pass with ease from the centre of infection into the surrounding tissues, and thence into the lymphatics and general circulation, whence they may be obtained within twenty-four hours. Where there has been a well-marked abscess-formation in the region of invasion there, as

already indicated, it is true that the microbes may be found outside the abscess at a fairly early period; but in the main, proliferation is limited to the abscess, and the blood remains free and sterile. Under certain conditions of greater virulence of the pyogenetic microbes it is found that as the abscess extends it becomes ill-defined—there is no sharp demarcation between the collected leucocytes and the surrounding tissue; the columns of leucocytes spread indefinitely from the centre, and numerous micrococci are intermingled with them. Where this is the case there is a marked tendency for the microbes to find their way into the general circulation from this irregular peripheral extension along the lymphatic spaces, and to set up a condition of septicæmia as in the more serous inflammation described above.

Septicæmia, or the passage of micro-organisms into the blood,[1] with all the results of such a passage—the condition which sundry French observers have described as inflammation of the blood—we shall not discuss here. In septicæmia we pass beyond the local response to injury, we deal with a state of general systemic disturbance. Nevertheless certain phases of the septicæmic condition throw light upon the inflammatory process.

In the first place, it is of interest to note that when the infective micro-organisms and their products are within the vessels they fail to induce the cardinal symptoms of inflammation. They do not lead to exudation of fluid from the blood or to widespread diapedesis of leucocytes. The stimulus, whatever it be, which leads to these phenomena at the point of invasion is no longer called into activity when the noxa is within the circu-

[1] This is the sense in which the term *Septicæmia* is employed by pathologists and bacteriologists; by some surgical writers the word is employed as synonymous with *Toxæmia*; to avoid confusion there is now a tendency to utilise the more precise term *Bacteriæmia* to indicate the presence of microbes in the blood.

latory apparatus. This is the reverse of what might be expected were the inflammatory process primarily due to a modification of the endothelium of the vessel-walls by the irritant, a modification passively permitting the exudation and passage outwards of the leucocytes.

This statement that infective micro-organisms and their products circulating within the blood fail to induce inflammatory changes, would seem to need modification when the development of *metastatic abscesses* is taken into account —of secondary abscesses, that is, in tissues at a distance, and not in direct continuity with the original focus. But a study of the mode of production of these abscesses shows that the statement still holds. Such abscesses originate round emboli of pyogenetic micro-organisms in the capillaries. Sundry cocci are arrested in a capillary, proliferate, and fill the vessel. It must not be thought that the plugging or embolism is an immediate process in these cases—that the bacteria are present in the blood in such numbers that a cluster of them, passing into a capillary, blocks it. Experience shows that, with a bacteriæmia of this extent, death ensues so swiftly that there is no time for abscess-formation. Either the bacteria are contained in a small mass of infected blood-clot, which is the immediate cause of the blockage (as, for example, in abscess of the kidney secondary to infective endocarditis, and in lung abscesses following upon suppurative thrombosis of the lateral sinus), or, in other cases, isolated bacteria passing with the blood into a capillary are taken up by a phagocytic endothelial cell, and, instead of being destroyed, multiply, lead to the death of that and surrounding cells, and form a colony occluding the capillary. It is only when a minute vessel is thus occluded that the abscess-process begins, that is to say, when by this occlusion the vessel has become extravascular; and while it is true that, primarily,

the arrest of pathogenetic microbes within the capillaries is often associated with a small accumulation of intravascular leucocytes and with degenerative changes in the vascular endothelium, the metastatic abscess, as such, forms not by accumulation of leucocytes in the occluded vessel, but around it; the leucocytes migrating from surrounding capillaries.

CHAPTER VI

THE GENERAL REACTION WHICH MAY ACCOMPANY INFLAMMATION

In the second place, through this study of advancing inflammation it is of interest to trace the very close relationship that exists between inflammation and fever. Besides the local changes here described, local injury is accompanied by systemic disturbances. These may be slight or grave. Take, for instance, progressive abscess-formation, or follow the development of a malignant carbuncle in man. At first the reaction is purely local, but very soon, long before any of the micro-organisms are capable of detection in the blood, there is a raised temperature and a slight febrile state, the fever becoming more and more evident as the local process becomes more and more extensive, until with the detection of the microbe in the blood the most severe fever, with constitutional disturbance, sets in. Local inflammation, then, without any other possible explanation than either the nervous irritation to which it may give rise, or the passage into the general circulation of the soluble products of bacterial growth and tissue-destruction, or both, may lead to the development of the febrile state. How large a share is played by these two possible factors it is difficult to say. That bacterial products injected into the circulation lead to the rapid production of the

febrile state rests on ample evidence; but whether these act directly by inducing increased cellular activity, or indirectly by stimulating the cerebral centres, we cannot absolutely say. As yet we have little accurate knowledge of the part played by the nervous system in the development of the febrile state. This, however, may safely be declared, that the more we study the continued fevers the more do we discover that these commence by a local inflammatory disturbance. The continued fevers of bacterial origin are, in general, the continuance, or rather the extension, of a primarily localised inflammatory lesion.

In this conception of inflammation as essentially a local process we find ourselves at variance with Ribbert (30), whose views have been somewhat widely accepted among German pathologists. Ribbert holds that "inflammation includes both local and general processes" (*loc. cit.* p. 11). He calls attention to the fever which may supervene in the course of inflammation, the active new formation of leucocytes, mainly from the bone marrow, and discharge of the same into the blood, whereby *leucocytosis* is set up, and to the increased development of bactericidal and anti-toxic substances in regions distant from the area of primary injury; also to the various degenerative processes in distant organs—cloudy swelling, fatty degeneration, etc.—evidently due to the diffusion of toxic substances either from the inflamed area or from organised bodies, such as bacteria, which have escaped from the zone of active inflammation. But at the same time he admits (1) that these general processes can be induced experimentally without there being any local disturbance, as also that (2) mild grades of inflammation may lead to no general involvement of the system. He acknowledges thus that the two are not inevitably and essentially united.

The logical outcome of such an inclusion of the general body disturbances into our conception of inflammation leads to a lack of anything like a boundary between the condition of inflammation and that series of general disturbances which for want of a better term we speak of as infection. According to Ribbert, inflammation must be made to include infection.

We see no "must" in the case; on the contrary, and we gravely doubt the wisdom of such teaching. One might as well banish wholly the idea of inflammation as a distinct entity. It appears to us both more sensible and more in accordance with tradition to hold that (1) inflammation is the *local* reaction to injury, (2) that this *may* or may not be accompanied or followed by systemic reaction, and (3) that this systemic reaction to injury covers so wide a field, including not only the discussion of fever, leucocytosis, anti-toxic formation, and the principles of immunity, but also (as Ribbert neglects to note) that of pain and shock, that advisedly it should be considered apart and then in several chapters. That in studying the phases of the local reaction we must repeatedly advert to the systemic reaction is one thing; it is another thing to regard systemic reaction as an essential part of the process.

CHAPTER VII

SUMMARY OF THE FACTS THUS FAR BROUGHT FORWARD

The main facts gathered thus far concerning the inflammatory process, and the conclusions to be drawn therefrom, may now be placed in order before I discuss in detail the various factors in the process. They are—

1. Injury, when it is not so widespread and severe as to lead to the death of the individual, is followed by a reaction on the part of the organism. This reaction may be (*a*) localised, (*b*) generalised; it is the first of these that constitutes inflammation.

2. In unicellular organisms the continued vitality of the individual after injury, and in multicellular organisms the vitality of the individual cells, is dependent primarily upon the persistence of the nucleus; if this be destroyed or removed the rest of the cell is incapable of complete restitution and continued growth.

3. In unicellular organisms the reactive process is twofold, and consists of (*a*) destruction or removal of the irritant; destruction being brought about by a process of intracellular digestion, removal by extrusion of the irritant; (*b*) new growth of the organism.

4. This response to injury on the part of unicellular organisms is essentially reparative.

5. In multicellular organisms, with division of labour among the constituent cells of the individual, there is a

separation of functions; the twofold local reaction to local injury is yet more clearly marked; but

(*a*) The destruction or removal of the irritant is *in the main* accomplished by the wandering cells of mesoblastic origin.

(*b*) The new growth to replace the tissue destroyed by the irritant proceeds *in the main* from the fixed cells of the tissue.

6. Ascending the scale of multicellular organisms, a division of labour and differentiation of function is discoverable among the wandering mesoblastic cells. Whereas in the lower forms of the Metazoa one form of leucocyte alone is present, in the higher forms two or more varieties can be distinguished which possess different properties and act differently towards irritants introduced into the system.

7. According to the nature of the irritant causing the injury, the leucocytes are actively attracted in greater or less numbers to the region of injury, surround the irritant, and remove or destroy it by means very similar to those employed by unicellular organisms. Where the irritant is present in the form of discrete particles, some at least of the leucocytes may incorporate the particles, and remove them or destroy them by a process of digestion. Others of the leucocytes in the higher Metazoa do not act thus as phagocytes; nevertheless they are equally attracted to the focus of inflammation, and presumably tend to counteract the irritant by some other (extracellular) means.

8. While to the wandering cells appears to be allotted the main duty of removing deleterious and irritant matters, certain of the fixed cells of the organism, notably the endothelial cells of the vessels, also exert these functions.

9. Among the very large number of Metazoan forms

in which no complete vascular system is present, this attraction of the leucoeytes to the region of injury is at first the sole recognisable response to injury, proliferation of the fixed cells occurring in the neighbourhood of the injury at a later period. The relation between leucoeytie migration and tissue proliferation is, however, a variable quantity; there may be active proliferation in response to injury with little evidence of wandering in of leucocytes.

10. Among the higher Metazoa, in which there is a well-developed vascular system, the determination of leucocytes to the region of irritation still continues, nay, more, is markedly aided by the participation of the vessels in the inflammatory process.

11. The vascular phenomena in inflammation may be regarded as serving two main purposes—(*a*) the pouring out of increased fluid into the injured area; (*b*) the afflux and diapedesis of leucocytes.

12. Even in the highest Metazoa, possessing fully developed vascular systems, the response to injury in a non-vascular area, such as the cornea, may be associated with no change in the surrounding vascular areas, but purely with a determination to the injured area of leucocytes already free in the surrounding tissues.

13. The second phase of the inflammatory process, that of tissue-repair, but very rarely occurs without evidence of previous migration of leucoeytes and exudation from the congested vessels; nevertheless with certain mild grades of injury it can occur.

14. A comparative study leads inevitably to the conclusion that the determination of leucocytes to the region of injury is the most constant and most characteristic early response to injury recognisable throughout the Metazoa, and that it must be regarded as the most important factor in the first stage of the inflammatory

process. The vascular phenomena noticeable in the higher Metazoa must be regarded as a second and highly important adjuvant factor of later development. New tissue-formation is the prominent characteristic of the later stages of the process.

15. As among the Protozoa, so in the Metazoa, the response to injury is consistently in the direction of repair of injury.

This general survey of the response to injury throughout the animal kingdom demonstrates most clearly that the same broad principles, the same methods of defence and repair on the part of the organism, are called into activity from the lowliest forms to the highest; that, in fact, no line can be drawn to separate one set of phenomena as truly inflammatory from another set which, while also a response to injury, is non-inflammatory. Although it is true that the term inflammation implies a reddening and congestion of the vessels, we find upon closer examination that reddening and congestion are not the fundamental but superadded features in the process of repair of injury—features superadded as the organism advances in its place in the animal kingdom. Thus if we are to comprehend the process satisfactorily, we must pass beyond the narrower acceptation of the term.

Having thus sketched broadly the general phenomena of the inflammatory process, it will be well now to describe in fuller detail the factors of this process among the higher vertebrata, and to bring together the more important results of the study of the respective functions of the wandering cells, the vessels, the fixed cells, and the nervous system in inflammation.

PART II

THE FACTORS IN THE INFLAMMATORY PROCESS

I.—THE PART PLAYED BY THE LEUCOCYTES

CHAPTER VIII

THE VARIETIES AND CLASSIFICATION OF THE LEUCOCYTES

As I have already shown, there is more than one form of leucocyte in the mammalian organism, and these several forms evidently possess different attributes, and act differently in the reaction to injury. Inasmuch as they have been variously classified—so variously, in fact, that it is often far from easy to collate the various descriptions and to discuss the forms distinguished by one observer in the terms of another—it is necessary to give the chief classifications of them and their relations.

The first to discriminate between the forms of white corpuscles in the blood was Wharton Jones (31) so long ago as 1846. He drew a distinction between

A. Granule cells—Finely and coarsely granular.
B. "Nucleated" cells—Non-granular.

These observations were confirmed and advanced by Max Schultze (32), who made out the following forms:—

1. Small round cells with round nucleus and little clear protoplasm.
2. Larger cells with round nucleus and more clear protoplasm.
3. Cells with finely granular protoplasm, and one, two, or more nuclei.
4. Cells with coarse granules in the protoplasm.

The distinctions drawn were, so far, purely morphological; and very little notice was taken of these varieties for a long period until Ehrlich (33), in a notable series of papers extending from 1878 to 1887, drew attention to the fact that the wandering cells of the organism react diversely towards the different aniline dyes, and possess diverse tinctorial affinities indicating chemical differences in the nature of certain constituents of the cell bodies. The granules of the previous observers were found to be variously affected by the dyes employed; they were shown not to be fatty, but—as Ehrlich put it—of the nature of a glandular excretion;[1] and comparing the effects of the two groups of aniline colours—that in which the dye is associated with the acid constituent of the salt and that wherein the dye forms the base (the "acid" and "basic" aniline dyes respectively)—he made out the existence of five forms of granulation associated with as many varieties of wandering cells. His table of cells, according to their granulation, is as follows:—

α. granulation—Eosinophil—Cells frequent in horse's blood, present constantly in small numbers in human blood; numerous in medulla of bones of rabbits, dogs, guinea-pigs, etc. Stain deeply with acid aniline dyes. Granules large and coarse.

β. granulation—Amphophil—Cells frequent in rabbits and guinea-pigs in blood; present also in medulla of bones. Stain both with acid and basic dyes. Granules fine.

γ. granulation—Basophil—Large cells found in the connective tissue, from the frog upwards, "Mastzellen"; in blood of man only in certain cases of leukæmia. Stain only with basic dyes. Granules coarse.

δ. granulation—Fine Basophil—The "mononuclear" leucocyte of human blood. Granulation fine. Stain with basic dyes.

[1] J. Weiss has studied the miero-chemieal reaetions of the eosinophilous granules, and eoncludes that they are of albuminoid nature; since they were found not to be digested in gastrie juice, he would ally them with the nucleins.

ϵ. granulation—Neutrophil—The most frequent leucocyte of human blood, polymorphonuclear or "polynuclear." Stain only in neutral dyes—not in acid or basic.

Ehrlich and his pupils and Rieder (34) have done much to throw light upon the relative numbers of the leucocytes possessing these different granulations in different diseases, but at first they accomplished little in discovering the origin of the various forms, their functions, or their relationships. We owe the first satisfactory studies upon the properties to the long-continued and wonderful series of researches upon Phagocytosis, initiated by Metchnikoff, who made out that the different wandering cells of the body act differently towards microbic and other foreign particles introduced into the organisms. Thus he was led to draw a distinction between—

1. Lymphocytes—immature leucocytes.
2. Large hyaline cells, mononuclear, phagocytic, "macrophages."
3. Smaller neutrophil cells, polynuclear, "microphages."
4. Eosinophil leucocytes—very rarely phagocytic.

English observers, notably Professor Sherrington (35), the late Dr. Kanthack (36) and Mr. Hardy (37), and more recently, following these, Dr. Durham (38), Professor Muir, and Dr. Beattie (39), have made notable advances in the determination of the function of the wandering cells in inflammatory and other conditions. Of American observers Dr. A. E. Taylor (40) deserves special mention. Kanthack and Hardy have materially simplified the classification given by Ehrlich by dividing the leucocytes of the blood into :—

1. Coarsely granular } Oxyphil cells. Staining with acid dyes.
2. Finely granular }
3. Coarsely granular } Basophil cells. Staining with basic dyes.
4. Finely granular }
5. Lymphocytes.
6. Hyaline cells.

Their coarsely granular oxyphil cells are the eosinophil cells of most writers; their finely granular are the neutrophil and amphophil of Ehrlich. They prove conclusively that Ehrlich's neutral stain is in no sense to be regarded as such, but must be considered as a weak acid dye.

Collation of the Classifications of Hæmatogenous Leucocytes by Different Observers

Kanthack and Hardy.	Ehrlich.	Metchnikoff.	Durham.
Finely granular oxyphil.	Neutrophil cell. / Amphophil cell.	Microphage.	Microxyeyte.
Coarsely granular oxyphil.	Eosinophil.	Eosinophil.	Macroxyeyte.
Finely granular basophil.	Basophil cell with δ granulations.	...	...
Coarsely granular basophil.	Mastzellen (γ granulations).	...	Coarsely granular basophil.
Lymphocyte.	Lymphocyte.	Lymphocyte.	Lymphocyte.
Hyaline cell.	...	Macrophage.	Hyaline cell. / Macrophage.

In connexion with this subject of inflammation yet another classification must be entered into. The above forms are all to be found in the blood-stream in the inflamed tissue. We have to recognise also other wandering corpuscles which are not necessarily derived from the blood. It may be questioned whether it is right to speak of wandering cells of tissue origin as leucocytes, that term having first been employed as synonymous with white blood corpuscles, but on the old presumption that practically all the wandering cells seen in inflammation are derived from the blood, it has been customary to speak of all orders of these cells by this name, and certainly their characters are such as to render it difficult to distinguish them one from the

other save with care. Thus as a matter of custom and of practical utility we elect to speak of all these various cells indifferently as leucocytes.[1]

Thus further we may divide the leucocytes concerned in the inflammatory process into the three following groups :—

1. *Hæmatogenous*, viz. those derived from the blood-stream; this includes polymorphonuclear (neutrophil and amphophil polynuclear) and eosinophil (coarsely granular oxyphil) and Mastzellen.

2. The *histo-hæmatogenous* include the lymphocytes and hyaline cells and other cell forms apparently derived from the lymphocyte. All these may either have passed into the inflammatory focus and the blood-stream, or may be the result of proliferation of cells already within the tissue.

3. The *histogenous* cells originate locally as the result of local tissue proliferation, and not by passage into the parts from the blood-stream.

The recent observations of Schridde (41), to which I shall refer later, indicate that improved methods of staining are capable of showing that there are distinctions to be made out between the lymphocytes of the blood and those of the perivascular sheaths, lymph glands, lymph follicles, and tissues in general. If this be so this class will largely disappear, and we shall be able to make a sharp separation between hæmatogenous lymphocytes on the one hand and histogenous on the other; all that will be left in the histo-hæmatogenous class being the hyaline cells of endothelial origin.

[1] Some modern workers like Schridde are attempting to confine the term leucocyte purely to the granular cells of the blood, and make a distinction between leucocytes and lymphocytes, which appears to me to be indefensible.

CHAPTER IX

HÆMATOGENOUS LEUCOCYTES

We need here say little regarding these, they are so fully discussed in all text-books of medicine and treatises upon the blood. We need but recall that the polymorphonuclear neutrophil cells are those which, passing from the blood, predominate in all cases of acute inflammation leading towards suppuration and abscess formation; that in human blood, as in most mammals, the eosinophiles while very characteristic are generally rare, though they may be noticeably increased in number in certain diseases, notably where intestinal parasites, trichinæ, etc., are present in the organism; the mast cells are a still rarer form. While such cells may occasionally be found in the blood, we are personally doubtful as to whether those seen in inflammatory foci have wandered as such out of the blood-vessels. Their granules are large and stain deeply with ordinary basic dyes such as methylene blue, and they must not be mistaken for small clusters of cocci.

HISTO-HÆMATOGENOUS LEUCOCYTES

Here, as above noted, we have first to consider the lymphocyte and its modifications. It is now accepted by practically all workers that the lymphocyte seen within the tissues and the small cell with round, deeply staining

nucleus so large as almost completely to fill the cell, and having a scanty ring of surrounding cytoplasm, may be derived both from the blood-stream and by proliferation of the lymphoid cells normally present to a greater or lesser extent, more particularly in the sheaths of smaller veins. Until recently it has been regarded as impossible to make a distinction between these two groups of cells. Now Schridde (by his modification of Altmann's stain) makes out very definitely that granulation can be made out in these cells, and that the granules of the hæmal lymphocytes are of a wholly different type to those seen in the tissue lymphocytes and the cells of lymph follicles, and, basing himself—with Ehrlich—upon the fact that the granules of the different varieties of cells are constant features of the same and present constant characters, he concludes that here we have to deal with two distinct cell varieties. The granules of hæmal lymphocytes he declares are very small, and of about the size of those seen in neutrophil leucocytes, and by his method they take on a brownish red tint. Those of the peri-vascular lymphocytes are larger, few in number, and of a pronounced red colour.

Plasma-Cells.—There is another form of mononuclear cell which must, we think, be included in this series, although, as to its properties and origin, there has been and still exists a very active controversy. This is the almost notorious plasma-cell. Unna (42) first named these in 1891, or rather misnamed them, using a term previously employed by Waldeyer for another form of cell. Unfortunately his description was not wholly adequate, and various later observers have evidently included and described under this term cells of more than one order, so that confusion is worse confounded. The cell which most closely conforms to Unna's description, and which, therefore, I regard as the plasma-cell

proper, has the following attributes:—it has a relatively small, round or oval, not indented nucleus, coarsely granular, rich in chromatin and, further, staining darkly; this nucleus is situated excentrically. The cell-body stains deeply with Unna's methylene blue; the shape within the tissues is liable to considerable variation—often rounded or oval the cells may be polygonal or even drawn out into a spindle; they are obscurely amœboid. As to the possession of phagocytic properties, opinion is somewhat divided. The general agreement is that they are not seen to take up bacteria; they may, however, contain inert particles of foreign matter such as vermilion or coal-pigment. As they grow larger and older, the cytoplasm tends to become somewhat vacuolated, and the nucleus to be less deeply stained. As to their eventual fate, nothing definite can yet be said at present. Cells having these characters are normally present in lymph-glands, spleen, and bone-marrow, and here every transition can be made out between them and the ordinary lymphocyte, which similarly, it may be noted, has a small, round, deeply-staining nucleus (even more deeply staining so as to appear homogeneous). According to von Marschalko (43), they may be noted in any inflammation within twenty-four hours. More recent observers state that they do not appear in quantity within the zone of inflammation until several days have elapsed. Now, as noted by Justi (44) and Councilman (24), there is normally around the veins a lymphoid sheath, and in inflammatory conditions this sheath becomes noticeably augmented. The cells here multiply by direct division, and, in addition, here and there mitoses are visible (Justi). That lymphocytes are endowed with faint amœboid activity (Wlassow and Sepp and A. Wolff (45)), and that, further, they migrate from the vessels, has now been pointed out by several

observers (Councilman, Almkvist (46)). It is quite possible, therefore, that the increase in the perivascular lymphoid sheath is in part due to migration from the vessels, and, therefore, that some at least of the hæmatogenous lymphocytes develop into plasma-cells. Though, admitting this, it seems to me evident that the majority of the plasma-cells are derived from the proliferating perivascular tissue, and thus are not immediately hæmatogenous. It is on these grounds that I am led to include them here in order to emphasise the fact that not all the leucocytes seen in the field of inflammation are of vascular derivation.

I have, I admit, here collated and selected out of a large number of very divergent descriptions those statements regarding the plasma-cell which conform with the conclusions I, personally, have reached regarding them. I am fully prepared to find that not all who have studied these cells will agree with what is here laid down, but to discuss the divergent views would occupy too much space. The reader, however, will find references to the leading papers bearing upon these cells given in the bibliography at the end of this study. The views here given in the main agree with those of von Marschalko, Paltauf (47), Justi, Mallory, and Councilman. In their properties the cells here indicated conform largely to Maximow's "polyblasts" (48), cells which Maximow regards as distinct from the plasma-cell.[1]

The views here laid down are largely supported, though at the same time considerably extended by Schridde, using his new stains, which, it may be added,

[1] Important as is Maximow's work, and obvious as is the amount of study given by him to the subject, I cannot but feel that in the tissues selected by him and by the methods employed he has failed to distinguish between young lymphocytes and cells of endothelial origin, and that, had he studied the peritoneum, for example, he would have reached other conclusions.

have the great advantage that by them it is possible to differentiate tinctorially the different forms of leucocytes present in the inflamed tissues. Schridde also sees every grade of development from the perivascular lymphocyte to the plasma-cell, though no relation between hæmal

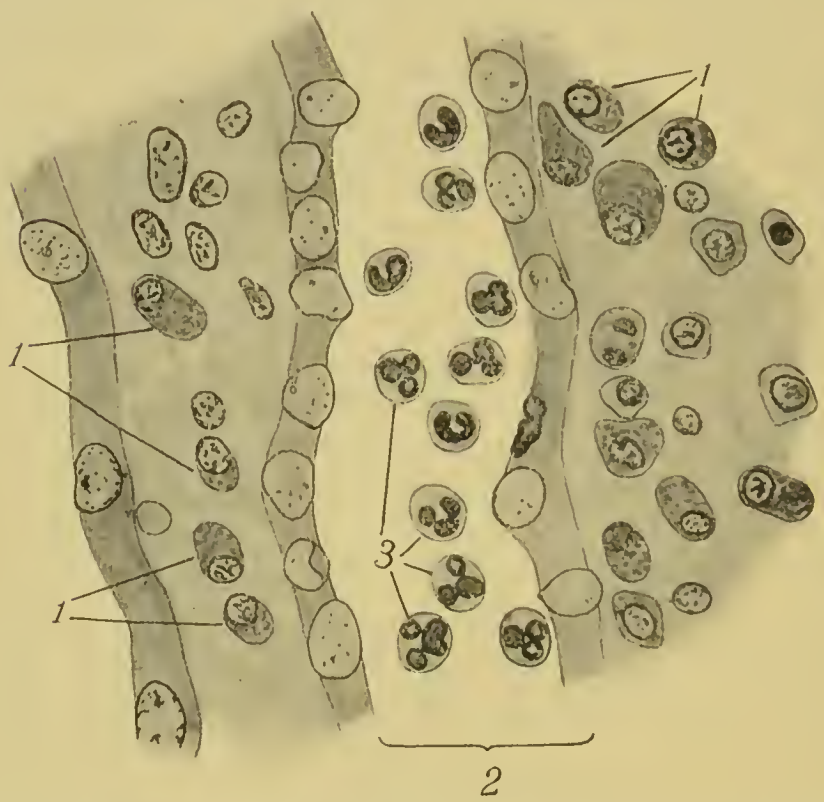

FIG. 5.—From a case of acute interstitial nephritis (man), drawn by camera lucida, $\frac{1}{12}$ Zeiss, ocular 2. Showing plasma-cells (1) in the interstitial tissue between the tubules. The epithelium of the middle tubule (2) is degenerated; the tubule contains polymorphonuclear leucocytes (3).—After COUNCILMAN.

leucocytes and this form of cell. He, however, goes further and finds three types of plasma-cells. The commonest of these is that with neutrophil granulations or weakly oxyphil. Rarer are those with acidophil or oxyphil granules (in which the oxyphilic character is somewhat less pronounced than is the case with the ordinary eosinophils); while the rarest of all are those

with metachromatic basophil granules corresponding to the mast-cells of the blood. We have thus, according to Schridde, two parallel series of cells—one derived in the main (in the adult) from the bone-marrow, thence gaining entrance into the blood; the other derived from the perivascular and lymph-follicular lymphocytes. These results need confirmation; I would only here say that, having seen Dr. Schridde's preparations and knowing his excellent technique, I am strongly inclined to accept his findings.

Hyaline Cells derived from the Vascular Endothelium.—We shall discuss these in connexion with histogenous leucocytes in general. Here we would only note that there is a certain amount of evidence that vascular endothelium can give origin to clear hyaline cells with little or no granulation.

CHAPTER X

HISTOGENOUS LEUCOCYTES

The part played by these is most clearly seen in the study of inflammation of the peritoneum. Many years ago Cornil and Ranvier (49) called attention to the very active proliferation of the endothelial cells of the great omentum in inflammations set up by the injection of dilute solutions of silver nitrate. They pointed out that these cells, flat and lamellar under ordinary conditions, become greatly enlarged with swollen nuclei which, within a few hours, undergo direct division, so that many cells come to possess two or three nuclei. Indirect division (mitosis) is only seen, according to Cornil and Toupet, in forty-eight hours. Some more recent observers have recognised it much earlier, Beattie (39) as early as the tenth hour. So swollen are the cells that they project prominently from the surface, being often pear-shaped and attached merely by a pedicle. As a result of the active proliferation, here and there large, semi-detached clumps of these cells may be made out. These authors did not study the exudate; this has been done by more recent observers, notably by Durham (38) and Beattie. The former, employing non-lethal intraperitoneal injections of several microbes, has described the same changes in the omentum as those described by Cornil and Ranvier, and has noted, more particularly, that these swollen cells

give origin, by direct division, to large, clear, mononuclear cells or leucocytes. These may be derived from the peritoneum generally, but the omentum is especially active in this respect. He identifies these cells with Metchnikoff's "macrophages," and Beattie has made a full study of the same. They are, according to him, the most characteristic form of leucocyte seen in peritoneal inflammation. After non-fatal peritoneal injection of the B. coli in the guinea-pig, he first observed an increase in the polymorphonuclear cells of the peritoneal fluid, which begins three hours after the injection and reaches its maximum in from six to thirty hours. Mononuclear leucocytes are first seen to increase in number about the eighth hour. On an average these are in numbers equal to or even greater than are the polymorphonuclears. From now onwards (in non-fatal as distinguished from fatal cases) they definitely preponderate. As during the next two days resolution proceeds, the polymorphonuclears become fewer and fewer until the few cells present in the exudate are almost entirely mononuclear. These mononuclear cells (the *hyaline* cells of the late Prof. Kanthack and Mr. Hardy, and of other observers) vary in size. According to Beattie there is every transition from small cells resembling lymphocytes with a round or kidney-shaped nucleus rich in chromatin, and with scanty protoplasm, up to cells four or five times as large, having a rounded or kidney-shaped nucleus which does not stain nearly as deeply as that of the smaller forms, but shows deeply-staining nodes of chromatin in the nuclear network. These larger cells have abundant cytoplasm, often showing extensive, fine vacuolation. In these respects the cells are identical with the swollen endothelial cells of the omentum. Nor are they merely passive agents—cells cast off in a moribund condition from the inflamed

peritoneum and undergoing degeneration. They are phagocytic; they take up bacteria, though, in this respect, they are not, with certain exceptions, so active as are the polymorphonuclears. Thus, if tubercle bacilli be injected, they are found, in a few hours, almost exclusively within the mononuclear cells and not in the polymorphonuclears. This is in harmony with our general experience that polymorphonuclear leucocytes, while not negatively chemiotactic to tubercle bacilli, are not potently attracted thereto, so that these more leisurely mononuclears have the opportunity to take them up. What is most characteristic is that these mononuclear cells are active cellular phagocytes; they take up other cells of the exudate—polymorphonuclears, eosinophils, and red blood-corpuscles. A single large mononuclear cell of a peritonitic exudate may often be seen containing three or four other cells or the remains of the same.

There can, therefore, be no doubt that, in peritoneal inflammation at least, an important series of free cells or leucocytes is of endothelial or tissue origin; the question is whether all these mononuclear cells are of like development. While clearly the larger forms are indistinguishable from the swollen cells of the peritoneal endothelium, and while the time of their appearance in the exudate coincides closely with the onset of active proliferation of that endothelium, we have the apparently contradictory statement that every transition is also to be observed between them and small lymphocytes; while other observers studying lymphocytes proper are equally convinced that these cells never develop into the large hyaline cells above described. Now lymphocytes proper may be found in the peritoneal exudate. These apparently contradictory results may be harmonised by pointing out that, in the first place, in the very earliest

stages, most cells are indistinguishable, and that, in the second place, a distinction can frequently be made out between the lymphocyte proper and the embryonic cell of endothelial origin. The former has a deeply-staining, rounded nucleus; the latter a nucleus which, while also deeply staining, tends to be indented. There is, however, another difficulty; if the omentum be examined during the period of peritoneal inflammation, its vessels are seen to contain mononuclear cells which, like these "hyaline" cells of the exudate, are devoid or almost devoid of granulation, and these intravascular cells are not to be distinguished from the medium-sized hyaline cells of the exudate. Why cannot some of the mononuclear cells of the exudate be hæmatogenous? There is, apparently, no reason why we should deny this hæmatogenous origin of some at least of these cells, nor would it seem that, making this admission, we land ourselves in further difficulties. On the contrary, the evidence accumulating of late years appears to point in one direction, namely, that the mononuclear cells seen within the vessels during the process of inflammation are similarly of endothelial origin. Metchnikoff, from 1883 onwards, was the first to suggest that the large mononuclear leucocytes seen in vessels and lymph-glands are identical in their properties and characters with the endothelial cells of these tissues, and he directed attention to their peculiar properties of ingesting other leucocytes, and named them "*Macrophages*" (a barbarous but a convenient term). Ruffer's (50) studies of the lymph-glands wholly confirmed these observations. The fullest studies upon the histology of these cells are by Mallory (51), who described, with great detail, the large cells with slightly-staining, grooved, or indented nucleus, present more particularly in the lymph-glands in typhoid fever, and possessing, in short, all the characters of Metchnikoff's macrophages. He describes them as

originating from the proliferation of the endothelial cells of lymph-spaees, lymphatics, vessels, and, in fact, all structures. He has observed their mitosis, and has demonstrated the migration of such proliferated endothelial cells into the adjoining conneetive tissue (Fig. 6). These observations were confirmed by Councilman in his studies upon keratitis (24). We have, indeed, to recognise the very active part played by the vascular endothelium in inflammation, its pronounced proliferative and phagocytic properties. As pointed out by Abbott,

FIG. 6.—Large cells of endothelial origin (macrophages of Metchnikoff) from centre of lymph-gland in typhoid fever which have actively taken up lymphocytes (*l.*) and red blood-corpuscles (*r. b. c.*).—MALLORY.

Nicholson, and myself (52), within ten minutes after inoculating the B. coli into the circulation, the endothelial cells of the liver capillaries are swollen and have taken up numerous bacilli (Fig. 7). Before our observations, Werigo (53) had demonstrated the process whereby hepatic endothelial cells give off pseudopodia, by which anthrax bacilli are seized and subsequently englobed. Recently Behring and Much (54) have called attention to the great phagocytic powers of the endocardial endothelium. As Beattie points out, in omental inflammation the cells lining the veins become swollen

and then detached from the wall, and various stages of the separation can be made out. Study of the sinuses of the spleen in typhoid (Mallory) shows the process very well; the lining cells swell to three or four times their original size and become separated, so that a sinus may become distended with these free cells. As they swell, their cytoplasm becomes vacuolated, and polymorphonuclears and other cells are seen to be ingested. Without entering into a discussion of the finer details of nuclear staining (*vide* Beattie's article) I would point out that the evidence now accumulating tends to the conclusion that Ehrlich's mononucleated non-granular

FIG. 7.—Endothelial cell of capillary of rabbit's liver, fifteen minutes after intravenous inoculation of culture of B. coli, showing bacilli ingested and undergoing disintegration. (The whole of the nucleus is not here in focus.)

blood-cells (33) are of endothelial origin.[1] Contrary, therefore, to Gulland, Saxer, and Uskow (55), I am of opinion that there is far from being a common origin for all the white blood-corpuscles; one group at least is of endothelial origin, just as another is of lymphoblastic. And thus, recognising that the former are capable of migration, it must be admitted that cells of this order seen in exudates may be of both local and hæmatogenous source.

A word may here be said regarding the fate of these large mononuclear cells. Evidence seems to show that

[1] With these I do not include the neutrophilic and other myelocytes seen in the blood in certain disorders: they, it need scarcely be said, are cells of a different order, clearly derived from the bone-marrow.

they do not, to any large extent, wander back into the blood-vessels. Various stages of degeneration of these cells may be recognised in the later stages of peritoneal inflammation; they tend to be extensively vacuolated, and thus the conclusion is that they in the main eventually disintegrate locally. While this appears to be true in connexion with bacterial inflammations, where more inert substances are taken up they clearly are capable of wandering in considerable numbers back into the circulation. Thus Metchnikoff points out that, if washed nucleated red corpuscles of the frog be injected into the peritoneum of a warm-blooded animal, large mononuclear cells containing the easily recognisable remains of the corpuscles can be detected after several days in the mesenteric glands, the vessels of the liver, and the spleen. Cells of the same order, which have not become free, evidently, according to Ranvier, take an active part in the formation of peritoneal adhesions. Muscatello, Graser, and Borst (56) unite in the opinion that the endothelium of serous surfaces can form connective tissue, though of late von Brunn (57) and Mönckeberg have strongly contested this view, at least as regards serous endothelial cells. Their objections are not, to me, wholly convincing. More recently Baumgarten (58) has brought forward what appears to be definite evidence that vascular endothelium under mild grades of irritation gives rise to fibroblasts and connective tissue.

Epithelial Leucocytes.—Mononuclear cells of endothelial origin seen in inflammation of solid tissues, noticeably in tubercle formation, are, from their general appearance, often spoken of as epithelioid cells. But if we employ the term epithelium, as is usual in English-speaking countries, to denote membranes derived from the primitive epiblast or hypoblast, this usage is apt to cause confusion. There are, however, true epithelioid

cells; I refer to the large phagocytic cells seen in pneumonic conditions, clearly derived from the flattened epithelium lining the air-sacs. With Pratt (59) we must recognise, in the pneumonic exudate, two forms of large mononuclear cells: (1) large cells, round or oval, with a crescentic, vesicular nucleus placed towards the periphery and apt to contain cell-inclusions, and (2) a cell present in the early stages of acute lobular pneumonia, larger than the polymorphonuclears, but not so large as the form just mentioned, but, like that, having a large, vesicular, indented nucleus and a very slightly granular protoplasm. These also are phagocytic, and Pratt expresses himself as doubtful regarding their origin. From his description, and since they are also found in the capillaries and in the tissues, it would seem clear that these are the endothelial mononuclear leucocytes mentioned above.

Free Cells — Leucocytes — derived from other Tissues. — In the experimental inflammations of the cornea it can be recognised that the tissue-cells of the boundary zone in which there is no actual destruction undergo active proliferation. The corneal corpuscles, for example, as already indicated, become swollen, send out processes towards the point of injury, their nuclei stain more deeply, undergo division, and now two young cells of embryonic type are present where one had been before (*vide* Fig. 3, p. 27). These young cells are of the hyaline or mononuclear type, and, what is more, like the cells of endothelial origin, actively take up polymorphonuclear and other cells. Nor are the connective-tissue corpuscles alone in giving rise to cells of this order. Highly complex tissue-cells, like muscle fibres, when injured, are apt to exhibit direct division and multiplication of their nuclei; these nuclei are apt to separate from the main mass, carrying with them a small body

of surrounding eytoplasm. This proeess in eonnexion with the degenerating tadpole's tail has been well described by Metehnikoff, Barfurth, Griffiths, and others (60). When so separated, these eells are not to be distinguished from hyaline mononuelear leueoeytes and, like them, aetively digest eell-debris, and so forth.

Clasmatocytes.—In eertain fine eonnective-tissue membranes, both in warm-and eold-blooded animals, there are to be seen eonsiderable numbers of large, apparently wandering eells, elongated or mueh braneheđ, with a rounded or elongated nueleus which Ranvier (61), on aeeount of their tendeney to eut off or leave behind them in their wanderings small remnants of protoplasm, has termed elasmatoeytes. Marehand (62) has ineluded them among his leueoeytoid eells. Aeeording to Ranvier, these originate as leueoeytes—*i.e.* are derived from the blood—whieh have beeome more or less stationary in the tissues, and, on one hand, in their proliferation may give rise to eells of the exudate, and, on the other hand, may develop into true eonneetive-tissue cells. While agreeing with Ranvier in this latter respeet, Marehand denies that they originate from ordinary leueoeytes, and regards them as identieal with what Saxer (63) has termed "primitive wandering eells," whieh ean give rise to leueoeytes and nucleated red eorpuseles. He thinks that by repeated division they develop lymphoeytes, and that they gain entranee into the eireulation as a form of mononuelear leueoeyte, and, as already stated, that they may take part in the formation of eonneetive tissue. Maximow eoneurs in holding that they may form fibroblasts and mononuelear "polyblasts." But now, as Lubarseh (64) points out, an identieal form of eell is to be found in keratitis, with the same remarkable long proeesses, which are apt to be eut off and lie isolated in the tissues. If we then ean

determine the nature of these cells, we may arrive at some conclusion between these divergent views, but here, I must confess, there are difficulties. Lubarsch regards the characteristic corneal cells with spear-like processes as derived from mononuclear leucocytes which wander into the part. Grawitz (65), on the other hand, holds that these cells are modified corneal tissue-corpuscles. Counelman, and before him Senftleben, are very clear in their descriptions of the way in which, in certain grades of keratitis, the peripheral zone of corneal corpuscles

FIG. 8.—Clasmatocytes. After (1) RANVIER and (2) MAXIMOW.

enlarge, send out processes into the necrosed area, and proliferate. This process we have just described. Their statements, thus, are in agreement with that of Grawitz.

It will be seen, reading over the description of these various forms of cells which we regard as histogenous, as distinguished from hæmatogenous, that certain features are common to all of them: the tendency to attain to large size; the amœboid character; the rounded, or, at most, kidney-shaped nucleus; the tendency to take up other cells; the liability, on the one hand, in proliferation, to give off wandering cells of the mononuclear type, on the other hand, to develop into fixed tissue-cells.

Taking all these facts together, it will be seen that the clasmatocytes group themselves with the histogenous group of wandering cells, and as such I must classify them. In short, much, if not all, of the controversy regarding these different forms of cells becomes assuaged if we regard the cells of the mononuclear type with relatively abundant protoplasm—the so-called hyaline cells—as of endothelial and tissue origin, whether they occur within the blood or in the inflammatory focus.

To those who have not followed the copious literature of the last few years these questions regarding the nature of the different forms of cells seen in inflammation may appear to be small and unimportant, and the controversy regarding them to be very petty. But much depends upon the proper solution of this question, more particularly as regards the nature of the new-formed tissue which develops in areas of inflammation, and the difficulty in arriving at correct conclusions is very great. Any one who has studied inflammatory tissues will find out that, at first, classification of the different forms of cells seen seems to be almost hopeless. As a matter of fact, the youngest forms of newly developed cells are often so exactly alike that no means at present at our disposal serves to distinguish them; hence, for example, the controversy whether the large mononuclear cells give origin to lymphocytes. It is only by carefully following the successive stages seen in the proliferation of any one form of cell that we can arrive at any conclusion, and then by a combination of methods, for the employment of only one or two methods of staining is apt to mislead.

Let me once more repeat that I am fully prepared to find that others do not agree with the conclusions here reached; nay, more, I would add that I am personally fully prepared to modify my views regarding these cells in the light of further research. In the meantime, to sum

up, let me say that the completed table of the leucocytes concerned in inflammation would appear to be the following :—

Hæmatogenous.	POLYMORPHONUCLEAR (polynuclear, finely granular oxyphil, neutrophil, and amphophil cell).	Originating in adult mammals from the bone-marrow, and migrating from the blood into the inflammatory area.
Hæmatogenous.	EOSINOPHIL (coarsely granular oxyphil, macroxycyte).	
Hæmatogenous.	MAST-CELL (coarsely granular basophil). Very doubtfully.	
Histo-hæmatogenous.	LYMPHOCYTE (? of two types).	Originating from lymphoid tissue and from vascular and other endothelia respectively; present in inflamed area *either* by migration from blood *or* as result of local proliferation.
Histo-hæmatogenous.	PLASMA-CELL (? histogenous).	
Histo-hæmatogenous.	ENDOTHELIOID LEUCOCYTE (mononuclear leucocyte, hyaline cell (in part), "epithelioid cell" (in part)).	
Histogenous.	EPITHELIAL wandering cell (large hyaline cell, in part).	Originating locally as result of local tissue proliferation.
Histogenous.	CONNECTIVE TISSUE wandering cell (including CLASMATOCYTE).	
Histogenous.	MUSCLE AND OTHER tissue wandering cells.	

The genetic relationships I would suggest are indicated in the following table :—

SCHEMA OF RELATIONSHIPS AND ORIGIN OF THE DIFFERENT FORMS OF WANDERING CELLS OR LEUCOCYTES FOUND IN THE INFLAMMATORY FOCUS.

	Bone Marrow (of Adult).			Lymph Follicles and Perivascular Tissue.		Other Tissues of Organism.
Vegetative Stage (Mother-Cells)	MYELOBLAST With basophil cytoplasm, without granules			LYMPHOBLAST With basophil cytoplasm, no granules		FIBROBLAST, SARCOBLAST, ENDOTHELIOBLAST, etc.
Intermediate Stage	Myelocyte with Neutrophil granules	Myelocyte with Oxyphil granules	Myelocyte with coarse Basophil granules	Lymphocyte (small)		Hyaline Wandering Cell (of inflammatory focus)
Adult Stage	Neutrophil Leucocyte	Eosinophil Leucocyte	Mast-Cell (of blood)	Lymphocyte (large, of blood)	Plasma-Cell (of inflammatory focus)	Adult Tissue Cells

CHAPTER XI

SUMMARY OF PROPERTIES OF DIFFERENT FORMS OF LEUCOCYTES

AND here, though in so doing I to some extent anticipate and refer to matters to be discussed in some detail later, it is most convenient to sum up briefly the facts determined regarding the parts played by these various forms in inflammation.

Polymorphonuclear Leucocyte.—In acute inflammation, when the irritant is not too intense, this is the form most often attracted to the focus of irritation, migrating most rapidly and in the greatest numbers. It is the characteristic pus cell; is actively phagocytic, particularly for bacteria; secretes bodies of the nature of enzymes and, either while active or in the process of dissolution, liberates antitoxic and antibacterial substances. It may—(1) wander back into the lymphatics or blood-vessels; (2) undergo dissolution and disintegration *in situ*; or (3) be ingested by the proliferating tissue-cells and mononuclear leucocytes. It has nothing to do with tissue formation (66).

Eosinophil Leucocyte.—This is also actively attracted, and that at an early period, towards the inflammatory focus, migrating from the surrounding tissues and also from the vessels, but it is never the preponderating cell present. In peritoneal inflammations it is found in great numbers in the omental vessels, and in sub-acute and chronic inflammations of certain tissues, such as the skin, may also be relatively abundant. Very rarely is it seen to ingest bacteria, so that, to all intents and purposes, it is non-phagocytic. Kanthack and Hardy (36) and Hardy and Wesbrook (67) have ascribed a secretory activity to these cells, associated with the

reduction in number and apparent discharge of the coarse granules, but later observers have failed to confirm their observations. The mode of action, therefore, of these cells remains unsettled. Opie has noted (68) that, during the course of various pyogenetic infections, this form of cell disappears wholly or in part from the peripheral circulation, and after injection of a variety of bacteria into the peritoneal cavity of guinea-pigs he noted a similar disappearance; but now, examining the mesentery, during the height of the infection, the eosinophils were found collected in the blood-vessels, actively migrating into the peritoneal cavity, where they were collected in considerable numbers upon the surface of the omentum. They clearly, therefore, have a part in the inflammatory process, but what that part is must still be considered undecided; while there are indications that they proliferate *in situ*, all observers agree that they take no part in the formation of new tissue.

Mast-cell.—This is seen particularly in sub-acute inflammations (the coarse basophil granules, staining intensely with carbol-thionin and basic aniline dyes, and taking on a metachromatic nuance, must not be mistaken for clusters of small cocci). The nucleus stains feebly, according to the usual descriptions. Professor Miller of the University of Missouri has shown me his preparations, and permits me to refer to them. They definitely show that what has been taken for a feebly staining nucleus is a court or area where once the nucleus had been. The actual nucleus undergoes disintegration and discharge. This cell is sluggishly amœboid, and may detach portions of its cytoplasmic processes with their contained granules along the track taken by its pseudopodia. Nothing has been made out regarding the activities of this form of cell, save that Maximow (48 *b*) shows that in the course of the inflammatory process it undergoes atrophy and disintegration (69). Professor Miller's studies confirm these views, and indicate further a complete want of relationship between the relative abundance of hæmal and tissue mast-cells in inflammatory states. Schridde indicates that this type of cell within the tissues is a rare variety of plasma-cell.

Lymphocyte.—This is only slightly amœboid, and does not migrate very actively from the vessels to the injured area in acute inflammations. It is, however, capable of this migration, and, in some chronic inflammations, is the preponderating cell ("small round cell"). It is found more particularly in masses around the vessels, and this as a result of—(1) migration; (2) proliferation of the pre-existing lymphoid tissue. It is not phagocytic for bacteria, but may ingest particles of inert matter. The small lymphocyte, with a scarcely noticeable zone of cytoplasm, may give origin to the

middle-sized lymphocyte, with more cytoplasm and deeper staining round or oval nucleus, and to the *plasma-cell* (71). There is no evidence that these plasma-cells are actively wandering, or that they return to the blood; they occur especially in connexion with the formative and chronic inflammations, but whether they actively participate in the formation of new fibrous tissue is still a matter of debate.

Histogenous Wandering Cells.—These appear in the inflammatory area in general at a definitely later period than do the polymorphonuclears and the eosinophils, and in certain forms of inflammation (*e.g.* of serous membranes) may become the preponderating type, exhibiting well-marked phagocytic properties, being not so active as regards most species of bacteria as are the polymorphonuclear leucocytes, but peculiarly active as regards other cells and cell-debris. They are sluggishly motile, and though those of vascular endothelial origin may migrate from the vessels into the tissues, they are rarely recognised passing back into the vascular system from the inflammatory area; they are apt to become vacuolated. They multiply both by direct division and mitosis. They may—(1) undergo local necrosis and disintegration; (2) may form giant-cells, either by plasmodial fusion or by direct division of the nuclei; or (3) may be active factors in the formation of new tissue. Certain forms (*e.g.* those derived from corneal corpuscles, and the clasmatocytes) give off frequently long pseudopodial processes.

A word should here be said concerning sundry cells of later development, appearing as a result of inflammation —giant-cells, Ranvier's cells, and Glugc's corpuscles. Of these the last are evidently leucocytes of the hyaline type which have taken up the fatty products of tissue-degeneration; the second—colossal cells breaking down with great ease—are of endothelial origin. Giant-cells would seem to be of more than one variety; some appear to be due to aberrant cell-growth, wherein the nuclei undergo division without the protoplasm of the cell-body following suit. The characteristic giant-cells of tuberculosis and chronic inflammation may now be said with fair certainty to be plasmodia, in all respects comparable to the masses of fused cells seen to form in the lower animals around foreign bodies, and by Kanthack

and Hardy around masses of bacteria in the lymph of frogs outside the body. The observations of Borrel (72), Duenschmann (73), and Faber (74) strongly support this opinion. Hektoen's careful studies tend also thereto (75).

CHAPTER XII

PHAGOCYTOSIS

In the case of most pathogenetic micro-organisms, after inoculation into the organism, a very considerable proportion are to be discovered, sooner or later, within wandering cells which have collected in the region of inoculation. I have already mentioned more than one case of this nature in discussing the comparative pathology of inflammation. Evidently under certain conditions one of the functions of certain of the leucocytes is to attack and incorporate bacteria. The leucocytes having these properties in mammals are more especially the polymorphonuclear and the non-granular or faintly granular mononuclear cells of endothelial and tissue origin; the former, as already indicated, migrating from the blood, coming more rapidly into action and being most active from a very early period in tissues abundantly vascularised; the latter, in the main of local development, becoming active at a later period, and then acting as phagocytes towards other cells as well as bacteria. It is, for instance, the polymorphonuclear cell which is found in overwhelming numbers in an extending subcutaneous abscess, and these are seen to contain great numbers of the micrococci.

The conditions leading to this phagocytosis have been worked out in remarkable detail by Metchnikoff. He has amply demonstrated that the microbes can be taken

up in a living condition. Thus, if the Vibrio Metchnikovi (a form closely allied to the cholera spirillum) be inoculated into the anterior chamber of the eye of an immunised animal, within a very few hours phagocytes are seen filled with the small, slightly curved vibrios. If now one such cell be isolated, placed in a drop of broth upon a cover-slip, made into a hanging-drop preparation and examined under the microscope, it is

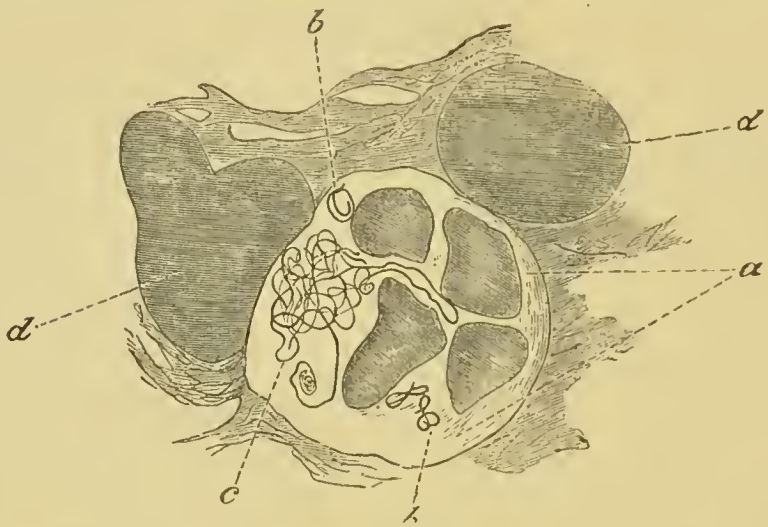

FIG. 9.—Resolution of acute infectious disease (relapsing fever) spleen pulp of monkey (a Macacus), showing (*a*) microphage, multinuclear, with incepted spirochætes; (*b*) solitary, and (*c*) forming dense tangle, (*d d*) nuclei of splenic tissue (Zeiss, $\frac{1}{8}$, ocular 4; × 1515 diam.).—METCHNIKOFF.

seen that the broth causes the death of the leucocyte; while with time, and favourable temperature, the microbes proliferate rapidly and completely fill the corpuscle until it disintegrates, whereupon they proceed to multiply in the surrounding fluid. This seizing and incorporation of microbes does not then necessarily lead to their death. In certain cases of acute disease there may be abundant phagocytosis, and the disease progress nevertheless; the phagocytes being destroyed by the products of the incorporated organisms. This is the case in mouse septicæmia, in swine erysipelas, and (as has been shown

by Gabritchewsky (76) in diphtheria. As Roux remarks: "Ils ont fait de leur mieux en englobant les microbes,

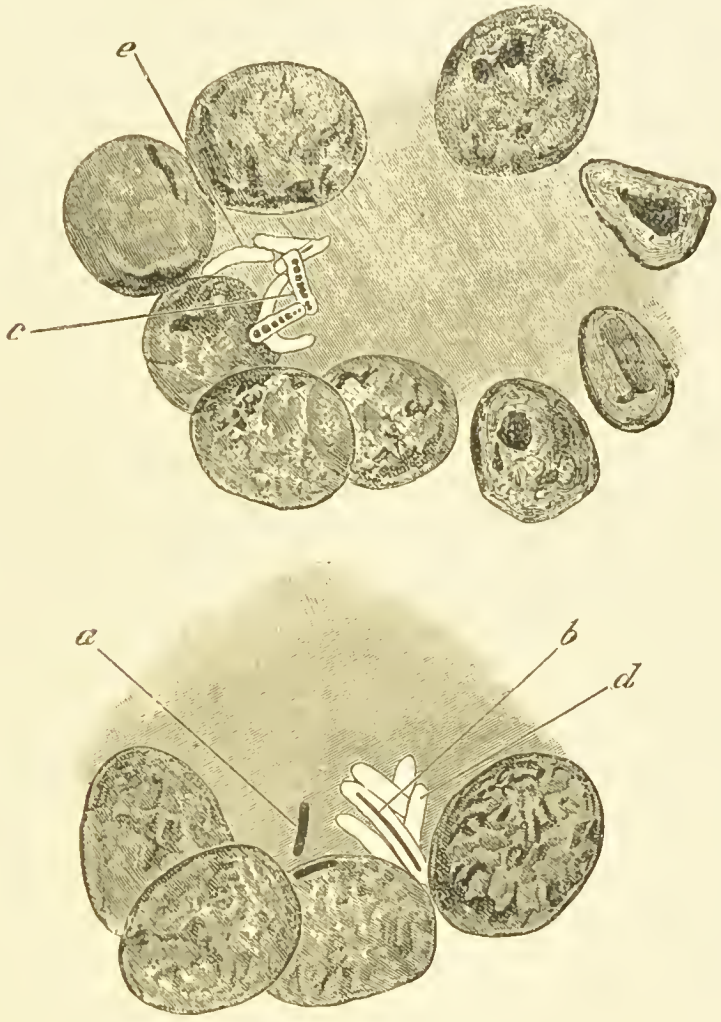

FIG. 10.—Two giant-cells, seen under high magnification (× 1515 diam.), from a rodent, the spermophile, inoculated with tuberculosis, to show stages in the destruction of the bacilli. *a*, unaltered bacillus; *b*, bacillus staining badly, and with greatly thickened capsule; *c*, bacillus granular and breaking up; *d e*, "shadows."—METCHNIKOFF.

mais ceux-ci se sont adaptés au milieu intérieur des cellules, et ils ont triomphés" (77).

In other less acute diseases, such as gonorrhœa, and in chronic maladies, such as in tuberculosis, leprosy, and

glanders, the bacilli may in certain stages be found within the cells and rarely free in the lymph-spaces, they appear to be almost parasitic, after the manner of the microsphæra previously referred to as infesting the amœba. In these cases it would seem as though the toxic properties of the microbes and the antagonising powers of the cells were nearly balanced. In tuberculosis, for instance, it is not unusual to find in the giant-cells some bacilli which evidently are undergoing degenerative changes, staining poorly and irregularly, or but faintly traceable as unstained, translucent shadows, while elsewhere they are apparently proliferating despite their intracellular position.[1]

And this equality, or almost equality of the resisting powers of cells and microbes may explain the chronic nature of the diseases above mentioned. Nevertheless, in general, it may be stated that there is some relationship to be recognised between the amount of phagocytosis and the virulence of the microbe; the more virulent the microbes, the less the proportion of them taken up by the cells, and the longer the time before the phagocytes come into action. As is the case in the unicellular organisms, so in the wandering cells of higher animals the process of destruction of the included microbes can, under suitable conditions, be seen to be digestive. Several observers have seen the anthrax bacillus, in frogs and other animals, wholly or in part surrounded by a vacuole developed within the leucocyte; and, as an evident result, the portion so surrounded has been seen

[1] It is, however, unsafe to declare in all cases that because a micro-organism continues to stain well therefore it was living at the moment the preparation was taken and fixed by heat. Thus in pneumonia after the crisis a fair number of diplococci may be found within the leucocytes of the expectorated contents of the alveoli, and these may stain perfectly well; yet it may be impossible to gain a single growth of the diplococcus from the same material.

to become swollen and fainter when stained, until it has undergone a veritable digestion and dissolution. By the use of appropriate reagents the vacuoles in general are seen to be faintly acid in contrast to the more alkaline surrounding cytoplasm.

As with the lower organisms, so with the wandering cells of the higher, there is an evident attraction, or chemiotaxis, whereby these cells pass towards the microbes and their products. The chemiotactic properties of the wandering cells have been especially studied by

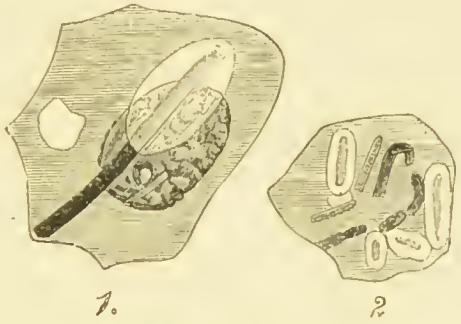

FIG. 11.—Phagocytes, macrophage and microphage, to show stages of digestion and destruction of bacilli, from spleen and eye respectively of white rat with anthrax. In *1*, part of the bacillus is unaffected, but a vacuole has formed around the other part, which further has now lost the power of taking the stain. In *2*, various stages are seen, the bacilli passing through the granular, badly staining, to the vacuolated, unstained stage, until finally but faint "shadows" are observable (Zeiss, $\frac{1}{18}$, oc. 3).—METCHNIKOFF.

Pekelharing (78), Leber (28), Massart and Bordet (79), and Gabritchewsky (76). Of the results obtained by these observers the most important are that leucocytes are variously attracted towards various substances. Thus Leber found that the introduction into the system of finely-powdered copper and various compounds of mercury caused an abundant collection of the wandering cells around the particles, while powdered gold, silver, and iron exerted no such attraction. Gabritchewsky and Buchner (80) showed that the products of bacterial growth in general possessed chemiotactic properties yet more powerful than simple chemical compounds. While the

degree of positive chemiotaxis is found to vary within wide limits, the examples brought forward of negative chemiotaxis exerted by bacterial products have so far been very few—so few as to support the contention of the late Prof. Kanthack (81), that it is very doubtful whether any microbes by their products actually repel the leucocytes, though they are capable of causing the rapid destruction of the attracted leucocytes, and so of rendering the area around the microbes relatively free from wandering cells.

This chemiotaxis would also seem in general to be in the inverse ratio of the virulence of the microbes. I say in general, for with chemiotaxis as with phagocytosis there appear to be exceptions to any uniform law; and cases can be brought forward—of diphtheria, for example—in which the leucocytes, instead of being repelled, are attracted in great numbers to the region of inoculation of a most virulent bacillus. Indeed it may be doubted whether it is the bacterial toxins as such that, diffused into the surrounding medium, constitute the force attracting the leucocytes towards the bacteria. We now have come to distinguish two orders of pathogenetic microbes, those which during active growth give off diffusible toxins, and those elaborating toxins which during active existence are not diffused, but remain intracellular (endotoxins) (82), so that the medium in which they grow has little or no toxic effects, although if the bacteria be collected and frozen at the lowest of temperatures and then crushed, their freed body-juices are found to be extraordinarily toxic. [MacFadyen and Rowland (83).] The diphtheria bacillus belongs to the first order, forms like the B. typhosus and the cholera spirillum to the second. It is only with the death of the bacteria of this latter order that the toxins are liberated to any extent. Now as regards chemiotaxis

and phagocytosis we can draw no line of demarcation between the two orders. Or, more accurately, up to the present there has been no adequate study of the interaction between leucocytes and bacteria of the exotoxic and endotoxic groups respectively. It is suggestive that the "type" producer of exotoxins, the diphtheria bacillus, induces active chemiotaxis and phagocytosis, followed by disintegration of the leucocytes, while the tubercle bacillus which characteristically gives rise to endotoxins is weakly chemiotactic, gives rise to a leisurely phagocytosis, and persists for long within the leucocytes without setting up pronounced reaction. The law would seem to be not that the extent of positive chemiotaxis is in inverse ratio to the virulence of the different species of bacteria as towards the human being or other larger animal, but that *with a given species of microbe* the greater the virulence of the strain the less the positive chemiotaxis. It has still to be determined whether it is the toxin as such, or some other diffusible substance produced coincidently, that attracts the leucocytes towards the bacteria.

A very good study of the action of bacteria of different degrees of virulence can be made by repeating an experiment of Metchnikoff. The rabbit is an animal susceptible to the growth within its tissues of the bacillus of anthrax. As is well known, there are various means whereby the virulence of this microbe can be diminished; so that if cultures of the "attenuated" bacillus be inoculated into susceptible animals, these, instead of causing a fatal disease, induce but a transient local inflammatory disturbance, accompanied by fever, and followed by complete recovery. If now a small quantity of a virulent culture of the bacillus be inoculated into the one ear of a rabbit, and an equal quantity of an attenuated culture into the other, the results are very instructive. Within twenty-four hours it can be noticed that an acute

inflammation has been indueed in both ears; in both the vessels round the seat of inoculation are greatly congested, but whereas at the seat of inoculation of the virulent organism there is a serous inflammation so intense that the skin is raised and separated from the subjacent tissues by a clear, transparent, reddish fluid which also infiltrates the deeper tissues, in the other ear there is not nearly the same amount of swelling and serous exudation; the region of inoculation is more opaque and solid. Upon more minute examination the serous fluid in the first ear is found to contain relatively very few leucoeytes; the firmer mass in the seeond is eomposed of a huge aggregation of lencoeytes.

Before proeeeding farther it will be well to sum up the phagoeytic hypothesis of inflammation as upheld by Metchnikoff and those who see in this phenomenon the all-important faetor in inflammation and the repair of injury (as also in the produetion of immunity), in order that, having put clearly forward the tenets of those upholding the hypothesis, I may the more readily state wherein lies the strength and wherein the weakness of the doctrine.

This hypothesis may be summed up in the following theses :—

1. That eertain of the leucocytes present in the blood and lymph, notably the polymorphonuclears (mierophages) and the large mononuclear hyaline eells (macrophages), are capable under eertain conditions of taking up baeteria whieh have gained entry into the system.

2. That in addition to these, the splenic corpuscles, the cells forming the endothelium of eapillaries, and other fixed cells of mesoblastic origin, possess the same property, although they exert it to a less extent.

3. That these phagoeytes seize upon and destroy living and aetive mierobes under eertain conditions.

4. That the more virulent the microbe the less the tendency for the leucocytes above mentioned, and for the other fixed cells, to take up the bacteria. The less virulent the microbe the more extensive the phagocytosis.

5. That in addition to this power on the part of certain cells (the phagocytes) to take up and destroy certain bacteria, another factor has to be called in to explain why the wandering cells of the body migrate towards the focus or foci where the micro-organisms have gained an entry into the body. This factor is the "chemiotaxis" exerted by the products of bacterial growth, and by some other substances, such, for example, as the products of death of tissue and of wandering cells, and experimentally also certain chemical irritants as, for example, turpentine and mercury. In the case of the virulent microbes the leucocytes are not attracted to the focus of infection. There is a "negative" chemiotaxis, and thus, in the absence of phagocytosis, the proliferation of the microbes takes place without hindrance; whereas the less virulent microbes and their products attract the leucocytes, they exert a positive chemiotaxis, so that there is a migration of leucocytes through the capillary and venous walls to the focus of infection, and the leucocytes taking up the microbes tend to arrest the infective process.

6. That the leucocytes may become accustomed and eventually attracted to substances from which at first they were repelled, and thus a negative may be transformed into a positive chemiotaxis.

7. That the cells, having once acquired positive chemiotactic properties in relation to the products of any specific microbe, retain and transmit these properties through a series of cell-generations, the length of which varies according to the microbe, the extent of the primary reaction, and the idiosyncrasies of the individual.

8. That, consequently, the cure of zymotic or mycotic disease, whether localised or general, and immunity also, are mainly brought about by the activity of special cells (the phagocytes), and are primarily dependent upon the attraction existing between these cells and the products of bacterial metabolism.

9. The process of inflammation is essentially the endeavour on the part of the organism to promote the migration of leucocytes, and to aid the inclusion and destruction of the irritant. "The essential and primordial element of a typical inflammation is a reaction of phagocytes against the irritant (*agent nuisible*)." Or, more fully, "inflammation is to be regarded, on the whole, as a phagocytic reaction of the organism against irritants,—a reaction which at times is accomplished by the wandering cells alone, at times with the aid of the vascular (fixed) phagocytes, or with that of the nervous system."

These are the main headings, if we may so term them, of Metchnikoff's hypothesis (for, to my knowledge, he has never formulated it clause by clause). Yet other data must be added to make it complete, data drawn from Metchnikoff's more recent studies (84), which we shall discuss in fuller detail later:—

10. The destruction of microbic irritants by the cells is a process of digestion, the cells elaborate ferments (cytases) which differ in their properties; that elaborated by the microphages (polymorphonuclears) is termed by him microcytase; that by the macrophages (hyaline mononuclears), macrocytase. These ferments are the main factor in the destruction of bacteria.

11. These ferments are formed and act within the living, active cell; they are endo-enzymes. But with the death and disintegration of the phagocytes (phagolysis) they become liberated, and, through their liberation, the body-fluids become bactericidal. Since cells which are

capable of acting as phagocytes liberate these cytases, the process is to be included as phagocytic.

12. It must be granted that when extracellular the cytases alone are incapable of causing bacteriolysis; bacterial destruction is brought about by the interaction of the cytase and another product of cellular activity—the "fixateur" (immune body or intermediary body). While the cytases are not specific, acting indifferently on various microbes, the fixateurs are specific, a different fixateur being developed in the process of immunisation against each specific microbe. These fixateurs are actively secreted from the living cell, and are present in the humours and exudates of the immunised animal. Metchnikoff has relatively little to say regarding these, but admits their existence, and further believes that they are developed from the same order of cells as are the cytases; hence he holds that they also are to be considered as results of phagocytic activity.

I have laid down these later theses somewhat in advance in order to present the doctrine as a whole, and that I may the more easily take up the objections that have been raised, some of which have been well met by Metchnikoff and his fellow-workers, though others still, in my opinion, have not been fully controverted.

In the terms of this hypothesis, then, phagocytosis is the all-important factor in the inflammatory process, the vascular, exudative, nervous, and other phenomena being auxiliary means whereby the phagocytic properties of the wandering and fixed mesodermal cells may be brought more fully into action: the determination of leucocytes that I have described is almost entirely to be attributed to an endeavour on the part of these cells to take up and destroy the irritant. To what extent is this doctrine to be accepted?

It must in the first place be laid down without the

slightest hesitation that phagocytosis is a factor in inflammatory processes; no antagonist of the doctrine nowadays is prepared to deny this. Nay, more, each succeeding year we recognise more fully that it is an important factor. There is not a single bacterial disease that affects man in which, to my knowledge, it has not been shown that the causative microbes are liable to be taken up by the cells, if not in man himself, at least in other warm-blooded animals. And, by repeating a very simple experiment devised by Leishman (85), this phagocytic activity of the human white blood corpuscles can very easily be demonstrated. It is only necessary to clean the finger, take a drop of blood, mix it with an equal quantity of a suspension of any pathogenetic organism, drop the mixture on a slide, place over it a cover-slip, place the preparation in an incubator at blood-heat for a quarter of an hour, then rapidly removing the cover-slip, fix the film and stain it by any good bacillary stain. Ordinary polymorphonuclear leucocytes present in the film can then be seen to have taken up, in this short time and under these not wholly favourable conditions, abundant bacteria. There may be twenty or more present in a single cell.

The Resistance Period.—It is when a hypothesis has been applied with the object of attaining practical ends, and is found to afford the results expected, that its value is proved, and we would point out that one of the most important recent advances in abdominal surgery has been developed from a basis of this hypothesis of phagocytosis. As already indicated, the injection of various microbic and chemical irritants into the abdominal cavity is followed by a pronounced leucocytosis, following upon which, when particulate bodies are present, there is seen to be abundant ingestion by the cells. Taking these facts into consideration, Issaeff (86)

determined that, if a peritoneal leucocytosis be induced by intra-abdominal injection of saline solutions, serums, etc., and then (twenty-four hours later) various species of spirilla be inoculated also into the abdominal cavity, the resisting power of the animal to these pathogenetic microbes is very greatly augmented. Dr. Durham (38) confirmed and showed that this was true, not only of the spirilla, but of the B. typhosus and other microbes. He found that the leucocytosis—and the increased resistance —lasted for some four or five days. Von Mikulicz and other surgeons have made use of this "Issaeff resistance period." A day prior to performing any serious operation, they inject nucleins, saline solutions, or serum, harmless in themselves, but capable of setting up an abundant leucocytosis. They have found that, thereby, they materially diminish the dangers of subsequent infection; the leucocytes, already in the peritoneal cavity in great numbers, take up and destroy bacteria which have chanced to gain entrance, before they have time to multiply.

One has but to read Metchnikoff's fascinating work on *L'Immunité dans les maladies infectieuses* (84), to be impressed with the extraordinary diversity and number of the researches in connexion with various pathogenetic organisms whereby the phenomena of phagocytosis have been established and confirmed. Yet, already in the course of discussion, there are one or two respects in which we are not wholly in agreement with the general terms in which the hypothesis is set forth. (1) We doubt, for instance, the actual negative chemiotaxis—the actual repulsion from bacterial irritants. At most, with Prof. Kanthack, we are prepared to see an absence of positive attraction. This, however, is a minor point and does not seriously affect the main question. (2) We have difficulty also in recognising that the extent of

chemiotaxis—and of phagocytosis—is in absolute inverse ratio to the virulence of the microbes. This obtains, we admit, in connexion with any one species; the more virulent the members of that species, the less the phagocytosis. But, comparing different species, it does not fully hold and, if virulence be dependent on toxic properties, then, when many of the most virulent bacteria do not diffuse out their toxins, we have to suppose that it is not the toxins but some other and diffusible substance, elaborated *pari passu* with the toxins, which is the cause of the attraction. Here again, while disagreeing, we do not think that this renders the hypothesis in its essence untenable. Granting this, phagocytosis might still be the all-important factor. (3) What deserves emphasis is that, by dwelling upon one function of the cells—that of phagocytosis—the hypothesis is incomplete. It is not permissible, in the first place, to expand the term phagocyte so as to include cells which do not eat, and if we agree that bacteria are destroyed and their toxins neutralised, not alone by intracellular but also by extracellular activities, substances being discharged into the lymph and blood plasma which arrest bacterial growth, neutralise the toxins, or lead to dissolution of the bacteria, then our hypothesis passes from being one of phagocytosis pure and simple into a "cellulo-humoral" one. Now we have to admit this, and, for a fuller comprehension of inflammation, have to appreciate duly all the factors that go to make up the very complicated picture. While we wholly agree with Metchnikoff that the later development of his hypothesis is a natural expansion, and while we understand the natural inclination to speak of it still as the phagocytic hypothesis, we find that the position is not clearly understood by every one, and the objection not infrequently raised that much that is now included in the hypothesis

is not phagocytosis at all, is difficult to controvert in a few words. It may further be urged with some justice that the extracellular and excretory activities of the body cells are minimised, and certain other factors in the process largely neglected.

This notwithstanding, Metchnikoff's views have been purposely given this prominence. It is through him and through them, and through the active controversy and critical research initiated by these remarkable studies, that we have reached our present standpoint regarding, not merely inflammation, but the wider subjects of infection and immunity. And what is more, they are in our opinion in the main incontrovertible.

Now, in order to arrive at what we personally regard as a wider and sounder view, it may be well to detail briefly and to criticise the more important of these researches directed against Metchnikoff's hypothesis.

CHAPTER XIII

THE HUMORAL HYPOTHESIS

The first strong attack—and that when Metchnikoff upheld an uncompromising phagocytosis and nothing else—was originated by Nuttall (87). So long ago as 1874, Traube and Gschleiden (88) had called attention to the antiseptic properties of the blood, and in his presidential address at the London meeting of the International Medical Congress in 1881 Lord Lister had noted that a drop of putrid blood, teeming with microbes, if diluted with a little water, when added to pure blood that had been received into a sterile vessel, might leave that blood unchanged for days, the blood remaining sweet and having, evidently, the properties of arresting the growth of the organisms of putrefaction. In 1887 von Fodor (89) of Buda-Pesth more definitely called attention to these bactericidal properties, but it was Nuttall, a Johns Hopkins student working under Flügge, whose exact studies called particular attention to the properties of the humours of the organism. In an attempt to repeat Metchnikoff's researches upon the destruction of the anthrax bacillus, this observer noticed that if he placed a fine canula containing a fresh culture of attenuated anthrax bacilli in the tissue of a rabbit's ear, there resulted in sixteen hours a rich cellular exudation; but phagocytosis appeared not to reach its maximum for twenty-two hours, and even then half of

the bacilli lay free and not taken up by cells; and he found, further, that the free bacilli showed involution and degeneration to the same extent as did the ingested. This led him to study the effect of blood-serum, defibrinated blood, and lymph upon the bacilli, and he discovered that these fluids had a remarkably rapid action, destroying great numbers within a very few hours. Nuttall's very full research appeared to show conclusively that the bacteria-destroying power resided largely in the serum, and that in inflammation the exuded fluid rather than the leucocytes brought about the destruction of the microbes. Further, Nuttall found that the bactericidal substance was destroyed by being subjected for one hour to a temperature of 55° C., so that blood-serum outside the body, thus heated, lost all its powers of arresting bacterial growth. A definite, if variable, quantity of bactericidal matter was present in a given quantity of the heated serum, capable of destroying a certain number of bacteria, so that, if more than that number were added, the excess survived and, in the course of a few hours, showed active multiplication. These observations were confirmed and extended by Nissen (90), Behring (91), and Buchner (93), and a most valuable series of contributions have been made by Hankin (92), Buchner, Vaughan (94), Tizzoni and Cattani (95), Behring, Ehrlich and his pupils (96), and others, upon the nature and properties of the substances to be derived from the blood-serum of animals either naturally immune to certain diseases, or rendered immune by one or other procedure. What is more, it has been recognised that two orders of substances are recognisable; one capable of destroying pathogenetic microbes, the other not destroying them, but rendering their products inert. We cannot here give these important observations in detail (84), as they bear more particularly upon the

subject of immunity. It was shown from several sides that, in the blood-serum and removed body-fluids as also under certain conditions within the tissues, there occurs active destruction of bacteria without the bacteria being ingested by the cells. The experiments were so clear, so easy to repeat and confirm, that we can well remember the time when, to believe in phagocytosis, even as an auxiliary process in the arrest and cure of disease, was to be regarded as to be lacking somewhat in common sense. The destruction of bacteria in the economy was held to be almost entirely—in some cases entirely—brought about by the action of the humours of the body.

But this humoral hypothesis pure and simple was soon seen to be inadequate. Its upholders could not say how and whence the bactericidal substance was derived, and the more sera were studied—whether gained from healthy animals, from individual cases of the disease, from animals naturally immune to certain diseases, or those rendered immune by inoculation of this or that microbe—the more impossible it became to recognise any sure relationship between the bactericidal power of the serum and the extent of resistance displayed by the individual affording that serum. It was noted also that the different humours of the body differed in bactericidal properties in a way that could not be adequately explained in the terms of this hypothesis.

CHAPTER XIV

THE CELLULO-HUMORAL HYPOTHESIS

If the serum and if the blood-plasma contain bactericidal substances, these must in all likelihood be developed by certain cells, and thus at bottom the humoral conception must be cellular; and the very fact of the great increase in the bactericidal properties of the blood immediately on its withdrawal from the body, must suggest that in the changes which occur in the extravascular blood there is a liberation and solution of bactericidal substances. Now the first and foremost of these changes is the breaking down of the leucocytes as the blood begins to clot. It may, therefore, be that this breaking down of the leucocytes, with liberation of their contents, is capable of explaining the increased bactericidal action of defibrinated blood and blood-serum. This, let me repeat, is not phagocytosis, at most it is a function of cells which can act as phagocytes. If correct, it seems that that group of wandering cells which more particularly exhibit phagocytic properties is also able to bring about the destruction of bacteria and the neutralisation of toxins by other means. As a matter of fact, evidence has steadily accumulated showing that more particularly the wandering cells of the body and also, probably, certain orders of fixed cells possess these other means. Many years ago Ribbert (98), in his studies upon the fate of spores of sundry species of mould (aspergillus and mucor)

inoculated into the anterior chamber of the rabbits' eye, had found that two stages of reaction were to be made out; at first the spores and developing hyphal filaments became surrounded by dense clusters of leucocytes which remained in apposition to but did not ingest the micro-organisms. They appeared to bring about a weakening and lowering of vitality on the part of the spores and filaments, so that, after a time, other cells wandering into the part could manifest their phagocytic action and take them up. Ribbert, it is true, attributed the lowering of vitality to the walling-in ("Wallbildung") of the leucocytes and consequent lack of nutrition. The fact remains that he demonstrated a preparatory extracellular action upon the micro-organisms by the leucocytes.

That the leucocytes contain bactericidal substances was first demonstrated by Hankin (92), who obtained from the lymphatic glands and spleens of animals immune to anthrax (dogs and cats), a proteid of the nature of a globulin, identical with Halliburton's cell-globulin β, and having a bacteria-killing power similar to that possessed by blood-serum. In later observations upon the rat he showed that there was a relationship between the amount and activity of these "defensive proteids" and the power of resistance of the animal to the disease. Thus Hankin showed that in animals possessing the power of destroying bacilli, the organs containing the largest collections of leucocytes yielded notable quantities of a bacteria-destroying substance. These defensive proteids are now more commonly known as alexins, this name having been given to them by Buchner, who, beginning as a strong supporter of the humoral hypothesis, ended in assuming a position which more nearly approached that of Metchnikoff. It was shown by Denys and Havet (99), of Louvain, that exudates rich in leucocytes have a more intense bacteri-

cidal power than has the blood-serum of the same animals, and that the blood and exudations of the dog freed from leucocytes, either by infiltration or by centrifugal action, lose their bactericidal power, regaining it when the leucocytes are re-introduced. Buchner (100) fully confirmed these observations. He showed that, if sterilised emulsions of the gluten of wheat be injected into the pleural cavity of a dog or rabbit, its presence leads to the pouring out of an aseptic exudation peculiarly rich in leucocytes, and this exudation is much more bactericidal than is the blood or the serum of the animal. He noted further that, like the alexins of blood-serum, this bactericidal substance of inflammatory exudates is destroyed by heating to 55° C. Several other observers (Bail (101), Schattenfroh (102), Van der Velde (103), Jacob (104), Löwit (105), and Bordet (106), have obtained similar results, employing various methods. Thus it is now generally accepted that the alexins or bactericidal substances of the serum, as of exudates, are derived very largely from the leucocytes, and that when, therefore, bacteria undergo destruction in the humours of the body without the intervention of cells, that destruction is indirectly due to the leucocytes.

Yet another line of work independently points in the same direction. Vaughan (94) separated from blood-serum nuclein, a body which so far had been found exclusively in connexion with the nuclei of cells. His work was independently confirmed and extended by Kossel. This nuclein is either itself bactericidal or has a bactericidal substance in association with it. The presence of such a body in the serum is best explained by the disintegration of nucleated cells, *i.e.* of leucocytes.

Clearly then leucocytes of certain orders contain bactericidal substances; can we recognise not merely a liberation of anti-bacterial substances by disintegrating

leucoeytes, but a functional active secretion of the same such as has been held by Kanthack and Hardy, and by Buchner and his school? Metchnikoff largely denies this; the microcytase and the macroeytase, the digestive ferments of the two main orders of leucocytes, are, according to him, endo-enzymes, acting with the cell-body and only discharged with the dissolution of the cell. At a very early period it was shown by Nuttall that the blood-serum removed from the body acts far more rapidly and energetically than does the blood-plasma and lymph within the body. The disparity of action between the two is remarkable. Thus Lubarsch (107) has shown that in order to kill a rabbit by intravenous inoculation of anthrax bacilli into the circulating blood, at least 16,000 virulent bacilli must be introduced. In other words, the whole circulating blood is able to destroy only some 16,000 bacilli at a time. On the other hand, a single cubic centimetre of the blood serum derived from such a rabbit can, outside the body, kill an even greater number of bacilli in a few minutes. The normal blood-plasma, therefore, does not appear to be actively bacteri-cidal, and this is confirmed by certain striking observations by Gengou (108). If rabbits' blood be obtained with every precaution against admixture with the body-fluids, be received into paraffined test-tubes, and be centrifugalised immediately so as to remove all the cells, a serum or plasma is obtained which will remain liquid for several days. So obtained, there has been a minimal breaking down of the leucocytes. This plasma has practically no bactericidal properties, but, on the contrary, serum from the same animal, obtained from blood allowed to clot, is actively bacteri-cidal. In this process of clotting there is, as we know, an extensive destruction of leucocytes.

But Gengou's experiments merely demonstrate that in the normal animal not subjected to bacterial invasion the

leucocytes circulating in the blood do not actively discharge bacteriolytic substances into the plasma: they do not controvert the possibility that, under bacterial stimulus, the cells of the body actively secrete these bacterial substances. It is, we confess, difficult either to prove or disprove that this is the case. If bacteria or their products be injected into the body-fluids, and these are found to become increasingly bacteriolytic, it may well be urged that the result is wholly due to resulting disintegration of the leucocytes. It must be noted further that other observers repeating Gengou's work (though often not his identical methods) have not gained such clear results (109).

Pfeiffer's Phenomenon.—A few years ago proof positive of such exudation, not by leucocytes, it is true, but by endothelial cells, seemed to have been discovered by Pfeiffer of Berlin (110). If a few drops of a pure culture of the cholera spirillum be injected into the peritoneal cavity of a guinea-pig, vaccinated against cholera, and, a few minutes later some of the peritoneal fluid be examined, it is seen that very few leucocytes are present, and, this notwithstanding that the spirilla, instead of having their usual curved "comma"-like form, have become globular, the majority staining badly and being dead. Outside the body the blood-serum of a highly immune guinea-pig has similar properties. If heated to 55° C. for an hour these properties are lost. There is, therefore, present in the peritoneal fluid, as in the blood-serum, a body of the nature of an alexin which clearly is, to some extent, responsible for this remarkable alteration in the spirilla.

It is impossible to deal in detail with the important controversy that has raged regarding the meaning of this Pfeiffer's phenomenon. Suffice it to say that Pfeiffer regarded the substance causing the phenomenon as an

excretion from the peritoneal endothelium; that Metchnikoff demonstrated that it was best explained by what he has termed "phagolysis"—by the rapid clumping of the leucocytes of the peritoneal cavity upon the omentum,

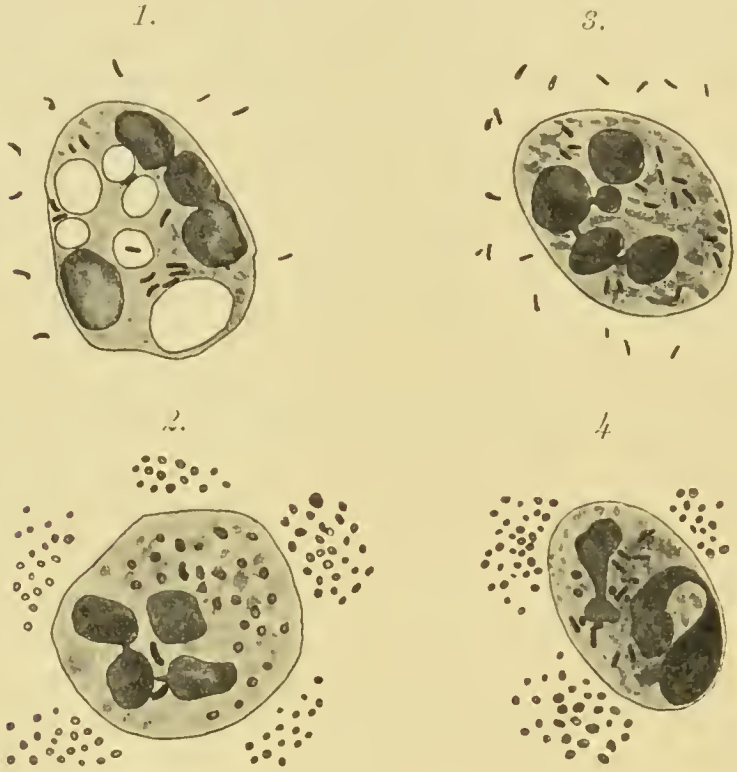

FIG. 12.—*Pfeiffer's Phenomenon.*—Effect of human blood serum upon spirillum cholerae (1, 2) and bacillus typhosus (3, 4) respectively.

In the two upper figures the blood-serum has been heated to destroy the intermediate bodies (immune bodies, opsonins). Leucocytes have been added, together with a suspension of the bacteria, and the mixture placed at 37° C. for fifteen minutes. It is seen that the polymorphonuclear leucocytes take up the unaltered bacteria. In the two lower figures are shown the effects of the *unheated* blood serum. In other respects the treatment is the same. Under the action of the serum the bacteria swell up and become spherical, losing their power of taking the stain. There is equally active phagocytosis. In the leucocytes are to be seen some unaltered bacteria. These have been ingested before the serum has acted upon them. —After WRIGHT and DOUGLAS.

followed by their dissolution and liberation of bactericidal substances; he has shown further that the phenomenon does not develop in connexion with body-fluids, such as the aqueous humour, containing few or no leucocytes; and that it does not occur if phagolysis be prevented;

while Bordet (111) demonstrated that the reaction needed the presence of two substances—an alexin or microcytase derived from the broken-down leucocytes, which is destroyed by heating to 55° C., and a second substance, not present in normal animals but present in the serum and peritoneal fluid of vaccinated animals, which is only destroyed at a temperature of 68 to 70° C. This substance belongs to the group of bodies which have been termed fixateurs, immune bodies, intermediary bodies, etc. In short, says Metchnikoff, it is the breaking down of the peritoneal leucocytes that is the main factor in bringing about Pfeiffer's phenomenon.

But where does the second substance, the intermediary body, which also is essential for the development of Pfeiffer's phenomena, come from? It is present, not only locally, but in most of the body humours. To be brief, there is no evidence that this substance is, under normal conditions, purely intracellular. The evidence, so far as it goes, is all to the contrary. As with the allied group of substances known as the agglutinins and the whole group of immune bodies produced in the development of immunity, these fixateurs or intermediary bodies are widely distributed in the organism, even in the excreta of immunised animals. They appear to be actively produced, and that over relatively long periods, and so we must conclude that they are products of living cells. This, at least, is the view accepted by all who have studied them, and, though he has singularly little to say regarding them, Metchnikoff's view partakes of this opinion (*vide* 84, p. 816). He regards them as also, in the main, produced by those cells which, under other conditions, act as phagocytes. This is, to say the least, doubtful. As Sir A. E. Wright (112) points out, the organisms which exhibit Pfeiffer's phenomenon under favourable conditions—notably the spirillum of cholera

and the B. typhosus—may be taken up by the peritoneal leucocytes very rapidly, before the phenomenon has manifested itself. When so taken up, they do not swell up and become globular, though others, ingested later, have a globular appearance. If the phagocytes themselves produce the intermediary substance, why should not the bacteria undergo like alteration *within* the bodies of the phagocytes? It is only outside these cells that the change takes place.

Wright's Phenomenon.—Where, indeed, these intermediary bodies are produced is, at the present time, an open question. That they play an important part is most evident, but, what is more, the recent observations of Wright and Douglas and other co-workers (112) show that, in connexion with the majority of pathogenetic bacteria, phagocytosis occurs with difficulty, if at all, in the absence from the body-fluids of certain of these intermediary bodies. These particular ones they have termed opsonins.[1] Wright and his fellow-workers confirmed the observation of Nuttall, Stern, and others that blood-serum has no bactericidal effect upon the pyococcus aureus. They were thus led to investigate to what extent active phagocytosis might explain the destruction of pyococci gaining entrance into the organism, and found that an active phagocytosis occurred, but only under certain conditions. If, along the lines of Leishman's experiment, the corpuscles are, by centrifugalisation, separated from the blood, and now a mixture be made of the washed white blood corpuscles, the serum, and a suspension of the pyococci, and this mixture be kept for a quarter of an hour at the temperature of the blood, active phagocytosis occurs; the polymorphonuclear leucocytes are seen to contain, each of them, numerous cocci. But if now, before making this mixture, the serum be heated to

[1] From *opsonò* (or *obsono*) "I cater for."

65° C. and then added, there is little or no phagocytosis. This points to the existence of something in the unheated serum which favours the process of ingestion of the bacteria, and, as a matter of fact, they show that a component of the active serum has a preparatory action upon the suspended bacteria, so that bacteria subjected to an unheated serum for a time and then placed in the heated inactivated serum are taken up more readily than those placed direct into an inactivated serum. They show, further, that in the process of rendering an individual more refractory to pyococcic infection, his serum comes to contain increasing quantities of this opsonin or intermediary substance. So that, taking the washed white blood corpuscles of an ordinary individual, adding these to a mixture of the serum of the immunised individual with a suspension of pyococci, the leucocytes of this *normal* individual take up a much greater number of the cocci in a given time than do washed white blood corpuscles of the *immunised* individual suspended in the centrifugalised serum of the normal individual, to which a culture of pyococci has been added. What is true of the staphylococci obtains also with the long series of other bacteria, the only exception noted being in connexion with members of the diphtheria group. These opsonins are found to be distinct from alexins or bactericidal substances, apparently distinct also from the ordinary intermediary bodies, for their activity is greatly lowered by subjection to a temperature of 55° C. But, as with the intermediary bodies, it seems improbable that they are secreted by the phagocytic cells. Sir A. E. Wright and Douglas found that the blood-serum of cases with abscesses might be from six to ten times more active in promoting phagocytosis than the serum extracted from the pus of the abscesses. If leucocytes secreted these substances, then we should expect that, in collections of leucocytes,

the reverse should hold good. A clear and full account of the experiments establishing the existence of opsonins and of their bearings has been given by Bulloch (113).

Here then phagocytosis is shown to be a most important factor in the destruction of bacteria, but another must also be included, *i.e.* the action of a substance not derived, it would seem, from the cells actively involved in the phagocytic process. It is interesting to note that the late Prof. Kanthack and Mr. Hardy (36), whose observations I quoted in a previous edition of this article as affording direct evidence that the leucocytes secreted

FIG. 13.—Granular (oxyphil) leucocytes attacking and coming into apposition to chain of *B. ramosus*. From a Ziegler's chamber preparation, peritoneum of guinea-pig. —KANTHACK and HARDY.

bactericidal substances, were the first to demonstrate clearly the compound nature of the bacteriolysis. Adding a suspension of anthrax bacilli to frogs' lymph and studying what happened, by prolonged examination under the microscope, they observed that cells possessing granules staining with eosin (amphophil cells) attacked the bacilli, coming into contact with them, and, in this process, the granules were seen to be discharged. These cells did not actively ingest the bacilli, but they, while remaining extracellular, showed evidence of degeneration. Only later and by another form of leucocyte was there, in the frog's lymph, active phagocytosis. In other words, according to them, one set of leucocytes secreted the substances acting upon the bacilli, and prepared these to be ingested by another order of these cells.

It must be admitted that these observers introduced not a little confusion by speaking of certain cells as eosinophilous, which as a matter of fact, correspond in most respects to the neutrophil and amphophil polymorphonuclears of the mammal, to cells which in higher animals are definitely phagocytic. Mesnil and others have been unable to confirm these observations; but then they have not repeated Kanthack and Hardy's experiments according to the lines laid down by them; they have attempted other methods. It must be admitted that in the frog the experiment does not always succeed. I have, however, made and seen preparations in which this loss of granulation and coincident degeneration of the bacilli could not be denied. We have not been able to convince ourselves that in the mammal the coarsely granular eosinophil possesses a like excretory function, although Kanthack and Hardy convinced themselves that this was the case. In his last confirmatory article upon this subject Hardy (37) calls attention to the fact that after contact with bacilli the coarsely granular oxyphil cells of the frog are diminished in size, and, what is more, that as the cells crawl over chains of bacilli they leave behind them a slime. Bacilli coated with such a slime never grow. The observations of Durham and others indicate a little-understood alteration in bacteria preparatory to ingestion, which, indeed, would suggest that the leucocytes of mammals do afford some preparatory secretion. If, for example, a relatively abundant suspension of actively motile but not highly virulent bacilli be introduced into the peritoneal cavity of an untreated guinea-pig and a drop of the peritoneal exudate be examined, it is noted at a certain period that while many of the bacilli are moving freely in the fluid, and may impinge with impunity upon the lymphocytes and eosinophil cells present, those that come into contact with

the hyaline mononnelears become arrested and motionless, and the individual leucocytes may be seen taking on a "hedgehog" appearance, the immobilised bacteria adhering by one end to the leucocyte. This adhesion and immobilisation, prior to ingestion, cannot, I think, be explained except by presupposing the existence of a zone of diffusible

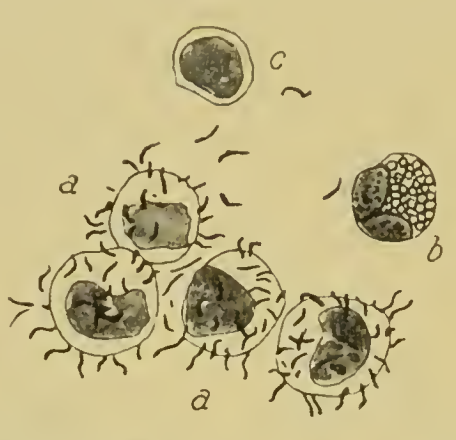

FIG. 14.—Leucocytes from peritoneal cavity of guinea-pig into which a microbe of low virulence (Sanarelli's "Versailles" vibrio) has been inoculated, to show "hedgehog" appearance around the mononuclear hyaline cells (*a*). The eosinophils (*b*) and the lymphocytes (*c*) were not affected (the polymorphonuclears—not shown—to a less extent than the hyalines).—After DURHAM.

material discharged from these cells and having a preparatory action upon the bacilli. Putting all the facts together, it would seem that, *under certain conditions, some preparatory or intermediary substances are separated from leucocytes of one or other order which aid in the process of phagocytosis, but the evidence is very far from conclusive that all the preparatory substances are of leucocytic origin.*

CHAPTER XV

SUMMARY

I AM thus led to modify Metchnikoff's conception of the mode of action of the leucocytes to some extent, and to believe that the following more nearly represents the state of our knowledge.

1. Phagocytosis—the process of ingestion and digestion on the part of the cells of the organism—is the factor most generally involved in the destruction of pathogenetic organisms within the system; both fixed cells, like those of the endothelium, and certain orders of free cells—leucocytes can manifest this property.

2. Where the cells are able to take up living bacteria, these cells have, in most cases, to be subjected to an extracellular action by substances present in the surrounding medium (opsonins) prior to digestion.

3. Bacteria may also undergo destruction without phagocytosis taking place. Where this is the case, the bacteriolytic substance (cytase) is liberated into the medium upon the death and disintegration of cells that are potentially phagocytes. It, however, cannot act without the intervention of a second intermediary body (fixateur) present in the medium.

4. Whether leucocytes and other cells of the body can actively secrete the bacteriolytic substance when stimulated, must be left an open question; it must,

however, be recognised that certain leucocytes secrete and discharge substances which, if not directly bacteriolytic, are preparatory to and essential for the destruction of the bacteria.

I have so far utilised Metchnikoff's terminology, using the term "cytase" for the intracellular bacteriolytic substances and, thereby, tacitly accepting the view that these bodies are ferments (the termination "-ase" being the conventional method to signify an enzyme). This is the view of the French school of bacteriologists generally. How far is this accurate? Other workers are by no means convinced that this is their nature. Pfeiffer and Ehrlich [1] regard the intermediary body or amboceptor as the ferment; and there is much to be said in favour of this view, but, so long as the nature of enzyme action is not clearly understood, so long as it is currently accepted that, in organic fermentations, only two factors are involved, for so long must there be confusion regarding what is the true ferment or enzyme. As a matter of fact, it would seem that in all organic enzyme action for the development of the complete cycle there are at least three factors requisite, and we have to decide which of these three is the ferment. The realisation that three factors are and must be involved immediately aids our comprehension of the facts here brought forward, and renders it easy to grasp the otherwise most puzzling order of affairs presented in the co-existence and mutual

[1] "Da unter dem Einfluss des Addiments (*intermediary body*) Erscheinungen auftreten, die man mit Pfeiffer als der Verdauung analog ansehen muss, so werden wir nicht fehlgehen, wenn wir dem Addiment den Charakter eines Verdauungsfermentes vindizieren."—Ehrlich und Morgenroth, *Ueber Haemolysin*. 1. Mitteil. *Gesammelte Arbeiten von Ehrlich*, p. 12. It is, however, but right to state that in more recent communications Ehrlich appears studiously to avoid any definite comparison between the bodies concerned in the production of immunity and the digestive and other ferments. I gather that at present he maintains an open mind in the matter.

action of the amboceptors and complements, of fixateurs and cytases, opsonins, lysins, *et hoc genus omne*.

The ferments of the body should not be looked upon as a special group of chemical compounds, but, on the contrary, enzyme action should be viewed as a property of a series of substances possibly of very different chemical composition. This view was seriously discussed by Woodhead (114) many years ago. The study of the catalytic action of finely divided platinum, of manganese dioxide, etc., supports this view. I am thus inclined to

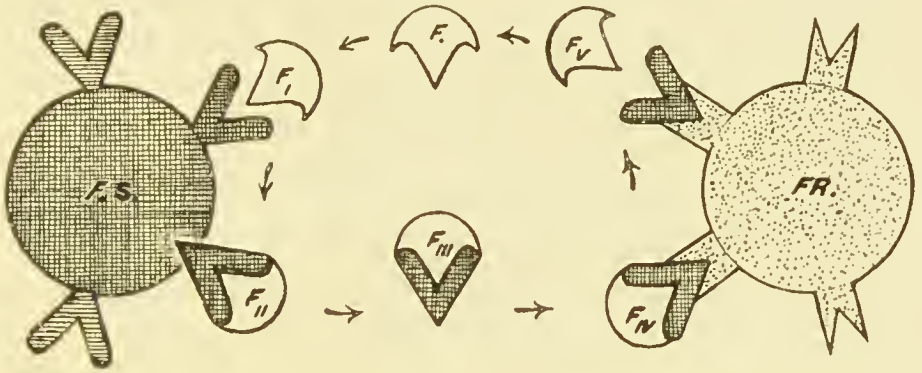

FIG. 15.—Diagram to illustrate the conception regarding ferment action and its application to the side-chain hypothesis of immunity. *FS*, molecule of fermentescible substance with side-chains; *FR*, molecule of fermentator; *F*, ferment; F_I F_{II}, etc., the successive stages in the action of the ferment.

consider that the ferments, or bodies presenting enzyme action, may be regarded as a certain order of unsatisfied molecules, which enter into combination with certain other molecules in the surrounding medium for which they have affinity; a chemical action takes place resulting in the enzyme becoming attached to certain atom groups of the fermentescible molecule. It is not even necessary to suppose that as the result of this chemical action, the atom groups are immediately detached. So soon as this union takes place, the enzyme molecule becomes satisfied, and, were there no other substances present to disturb the equilibrium, further

aetion would cease. For ferment action to continue there must be some third substance present, which we may term the fermentator or eomplement, having an affinity for the atom group represented by the ferment plus side-chain, or atom-group, of the fermentescible substance. As the result of its presence, a second union takes place, and what had been the unsatisfied atom-group of the fermentescible substanee of the above eompound, becomes now attached to and eombined with the fermentator. The ferment beeomes free, onee more unsatisfied, and ready to aet again on the fermenteseible substanee. We may go farther and suppose that the atom-group or side-ehain of the fermentator thus modified by eombination with the atom-group from the ferment-eseible substance, may either remain attaehed to the fermentator (complement) or become liberated as a separate entity.

Aeeording to this coneeption of ferment aetion, which is the ferment—the intermediary body (fixateur) or the lysin, complement or cytase? Clearly, I think, the former; the eytase ean only be regarded as the fermentator, the substanee essential for the final aet in the process. And this view is supported by Wright's phenomenon, in which the baeterial bodies must have the intermediary body (opsonin) in association with them before they ean be acted upon by the cells. Possibly it is a matter of convention which we shall term the enzyme or ferment, whether the intermediary body or the third substance essential for the eompletion of the process. Yet it seems more just that the aetive factor in the process should receive the name; just as, with Pawlow and Bayliss and Starling (115), and in opposition to Metehnikoff and Delezenne (116), I would lay down that in tryptic digestion the enterokinase is the trne ferment, and would regard the trypsinogen as the

fermentator. And thus, to sum up, I find myself in harmony with Pfeiffer and Ehrlich in regarding the amboceptor or intermediary body as the ferment, and, in place of speaking of the cytase of the phagocytes, would speak of the cytolysin or the bacteriolysin.

To complete this section I will here add other conclusions deduced from a study of the later stages of inflammation and discussed in a later chapter ("Upon the part played by the fixed cells in the Inflammatory Process"), viz. :—

5. In the later stages of inflammation the growing fibroblasts may often be seen to contain leucocytes in process of digestion. Presumably, therefore, a certain number subserve nutrition.

6. Others are, in certain cases, recognisable in the lymph-spaces outside the inflammatory focus, containing the debris of dead tissue. Emigration can therefore occur as well as immigration.

7. The process of development of wandering into fixed cells has been observed; cells of what are here termed the haematogenous type have never been observed to become thus converted; the histogenous alone would seem able to undergo the change.

8. The contrary process of development of wandering cells from degenerating tissue (muscle-fibres) has also been recorded by more than one observer.

II.—THE INFLAMMATORY EXUDATION

CHAPTER XVI

THE FLUID OF THE EXUDATE

Whenever injury to the tissues leads to vascular dilatation there is an increased effusion of fluid from the blood. The extent of this effusion varies greatly; it varies with the tissue affected, the state of the organism, and the quality and nature of the irritant. Dense tissue permits of little exudation, while loose vascular tissue, under the action of an irritant of no great intensity, may undergo great exudative swelling. There is, for instance, a peculiar liability in serous and cutaneous surfaces (or more truly in subserous and dermal layers), when inflamed, to manifest abundant exudation. Their vascularity and the slight external resistance would appear to explain this liability. There is a like tendency to abundant exudation from mucous surfaces, though here to a large extent, so long as the covering epithelium is not destroyed, the exudation is governed—*i.e.* partakes of the nature of an excretion, abundant mucus from the cells being also discharged, and is not extreme. With destruction of the covering epithelium it may become profuse; choleraic diarrhœa is perhaps the most pronounced case of exudation in the human organism. That some general state of the organism is a factor concerned

is seen when virulent anthrax bacilli are inoculated subcutaneously into an ordinary rabbit and into one that has been rendered immune: in the former the exudation is of a serous nature, in the latter little fluid is exuded from the vessels—a clear indication that, in the development of the immune state, not merely the leucocytes, but also the capillary walls, at the least, become altered in their behaviour to the toxins. The effect of the quality of the irritant is observable upon comparison of the results of inoculation of various microbes. Some cause little exudation of fluid. These are in general of low pathogenetic quality, but not always; certain virulent microbes (such as those of tetanus) lead, when inoculated, to relatively little effusion of fluid from the vessels. On the other hand, it may be stated definitely that where in a moderately dense tissue the injection of a pure culture of a micro-organism leads to well-marked exudation, the micro-organism is of high virulence.

Can any meaning be ascribed to this effusion, or, to express the same idea in words which shall not offend those who fear the semblance of teleological ascriptions, has the increased pouring out of fluid into the tissues as the result of irritation, been of proved benefit to the species, so that those individuals have survived who have manifested this reaction and have conveyed it to their offspring? Is it an attempt at increased nutrition in the injured region? It has been suggested, in accordance with Virchow's conception of inflammation, that the injury, stimulating the surrounding fixed cells, leads to increased local metabolism; and that the exudation is a means of bringing to the region the increased nourishment demanded by the increased cellular activity. But inasmuch as exudation is most marked in those cases where there is most profound and rapid cell destruction,

and again at the early stage of the inflammatory reaction, when evidences of growth and proliferation of the fixed cells of the region may be, and most often are, wholly wanting, this view can scarcely be upheld. Yet at a later period of the process, and again in chronic inflammation, the overgrowth of the connective tissue-cells would appear to stand in some relationship to the over-nutrition caused by the continued dilatation of the vessels and the pouring out of excessive lymph into the tissues. It must, however, be admitted that the exact relationship subsisting between nutrition and cell overgrowth is still a matter of debate among pathologists.

That the exudation exerts a "flushing-out" action is very evident in many cases. Thus the inflammation induced by plunging an animal's leg into hot water is accompanied by great increase in the amount of lymph obtainable from the efferent lymphatics of the part. Experimentally it may be shown (Samuel (117) and others) that seven to eight times as much lymph may drain away from an inflamed as from an uninflamed region. It is shown also by the presence of streptococci in the lymph channels outside the area of acute inflammation in erysipelas, by the frequent implication of the nearest lymph-glands in suppurative disturbances, and by the appearance of lesions, due to the direct action of bacterial products, in organs far removed from the focus of bacterial proliferation in such diseases as diphtheria and tetanus, wherein, as a rule, the bacteria remain strictly localised. It is clear that the exudation into an inflamed area may be much in excess of the normal transudation; that it can accomplish a removal of irritant matters. It is clear also, from more than one of the examples given above, that a process which may be beneficial to the region of injury may be harmful to the system as a whole.

Study of the "flushing-out" effects of the inflammatory exudate affords, in fact, a good object-lesson as to how far the reaction to injury is to be regarded as purposive. Yet we are forced to see that there is a certain amount of adaptation. Where the irritant can be conveyed to the exterior an abundant exudative inflammation generally occurs—an abundant flushing; where it can be conveyed into one of the body cavities the same holds good; but here a mechanism is often called into action (deposit of fibrin) whereby the exudate with its contained irritants is held within the serous cavity for days and weeks after all signs of active inflammation have subsided. The organism, that is to say, would seem to restrain its drainage to the general lymphatic system. Where the irritant is merely the product of tissue-change the profuse exudate is rapidly conveyed away; where, on the other hand, the injury of bacterial origin, the passage of lymph from the focus of inflammation, is, generally speaking, not nearly so free; it is of thicker consistency and drains away slowly. In short, as I have already indicated, where the microbe is not too virulent a cellular rather than a serous inflammation is produced; and in place of abundant flushing an increased antibacterial and antitoxic action of the exuded lymph comes into play.

But besides the mere "flushing-out" the exudation has often another effect, namely, dilution of the irritant and reduction of its injurious properties, so that it acts with lessened force upon the tissues, and permits the wandering cells to be attracted to the region where they may exert their functions. Where a comparatively mild physical irritant leads to abundant exudation the flushing-out action appears to be in the ascendant, where microbic irritants cause great local inflammatory œdema, judging from the less extensive lymph flow from the region, the diluent action must be regarded as the more important.

I have already pointed out that a relation may be traced between the intensity of bacterial irritation and the extent of the exudation. In short, there may be great exudation under two apparently opposed conditions: in the presence of comparatively mild physical irritants, and in that of severe bacterial irritants. In the former case it more especially subserves removal, in the latter dilution of the poison.

That in general the exudate exercises a beneficial effect upon the process of an acute or subacute inflammation, and that in general this is inadequate rather than excessive has been brought home to us of recent years by the remarkable success which has followed Bier's method of treatment (118), when properly carried out. This treatment consists in the production of a moderate grade of increased hyperæmia in the affected part whether (1) by the application of compressing bandages above the part, so that the free return of venous blood is obstructed, (2) by cupping, so that the lessened pressure causes determination of blood to the part, or (3) by the local application of heat as from electric or hot air baths, leading to increased vascular dilatation. All these means, indeed, bring about dilatation of the capillaries, thinning of their walls, and increased pouring out of fluid into the tissues. The swelling and redness of the part increase, but the patient benefits. Care, it is true, has to be taken and each individual case treated upon its merits; there must also be alternation of periods of treatment and rest. If properly carried out, as the part becomes swollen the sense of local pain disappears, and it is replaced by a feeling of general well-being, the inflammation ceases to extend, and actual absorption takes place of the inflammatory products.

How does this treatment bring about its good effects? Since corresponding results are gained whether we slow

the circulation by compression or increase it by the local application of heat, it seems scarce likely that increased passage of leucocytes into the part is the essential process. On the other hand all these methods favour the increased passage of fluid exudate into the affected tissue. It is to this that the good effects are to be ascribed, more particularly to dilution of the irritant and conveyance to the part of an increased amount of antibodies. We can to some extent harmonise the good effects gained by Bier by his treatment with those coincidentally gained by Sir A. E. Wright in his opsonic treatment [1] by supposing that increase in the exudate means increased amount of opsonins brought to bear upon the bacteria setting up the inflammation whereby these are prepared for ingestion by the leucocytes present in the inflammatory process. Certainly the exudate contains opsonins; these pass, that is, out of the blood-plasma into the tissues.

[1] Wright's treatment cannot be used for very acute cases, but has been found valuable in subacute and recurrent conditions. It is based upon the inoculation, subcutaneous, of accurately graduated amounts of dead cultures of the microbe that has caused the specific form of inflammation. The results of such inoculations are that the "opsonic index" or relative amount of opsonins in the blood serum (and so in the body fluids) becomes definitely increased, and with this the capacity of the organism to withstand the growth of the specific microbe.

CHAPTER XVII

THE SOLIDS OF THE EXUDATE: FIBRIN FORMATION

The fundamental characteristic of inflammatory exudation as compared with ordinary lymph is its richness in proteins. Whether we regard lymph as a filtrate pure and simple from the blood, or follow Heidenhain in regarding it as the result of a selective filtration, it is highly probable that in inflammation the exudate approaches in its composition more nearly to the blood-plasma than does ordinary lymph. The dilatation of the capillaries, the consequent thinning of the endothelial layer with, it may be, the opening of some lacunæ between the individual cells, and the direct action of the irritant upon these cells, may all be expected to aid the transudation. In this way the amount of protein matter in the lymph may be increased. But equally important must be the addition of proteins due to the breaking down of leucocytes and tissue-cells. I have already discussed this destruction of the cells, and need not here give the evidence of its occurrence.

This increase in the solids, mostly proteids, of the exudate, has been well shown by Samuel, by measuring the flow of lymph from the main lymph-channel of the dog's foot. In one such experiment he found that there was discharged in successive periods of three hours:—

1. Untreated foot; 4·0 c.cm. lymph containing 4 to 5 per cent of solids.

2. Foot subjected to venous obstruction; 28·5 c.cm of lymph containing 2 to 3 per cent of solids.

3. Foot inflamed; 28·5 c.cm. of lymph containing 7 per cent of solids.

The figures in the third case—of inflammation—do not represent the whole exudate. So thick was the lymph that it tended to clot and obstruct the canula, and there was, in addition, much œdema and swelling of the foot. But obviously, as Ainley Walker (119) points out, from twenty to thirty times more proteid matter may drain away from an inflamed than from a healthy region.

In addition to the proteins the inflammatory lymph may contain other substances worthy of more than passing note. Of these the more important are ferments, the results of proteolysis (notably fibrin and its precursors, nucleo-albumins and albumoses), and in many cases mucin, together with bactericidal substances, and, where bacteria are present, the products of their growth. Various extractives have been noted. Exudates rich in cells and disintegrated tissue-products—pus, for example, —may contain glycogen, fats, and, as Klotz working in my laboratory at M'Gill University has recently shown (120), a very definite amount of soaps.

The presence and amount of these substances depend largely upon the intensity and character of the inflammation. Thus the total quantity of proteins, and the proportion of fibrin, albumin, and globulin present, vary within wide limits. The following table[1] of observations made by Halliburton (121) shows well this variation in proteins, and the difference existing between inflammatory exudations and dropsical effusions:—

[1] These figures are thoroughly in accord with those of other analyses by Reuss, Hofmann, Mehu, and Letulle (122).

Pleural Fluid from	Sp. Gr.	Percentage Quantity of			
		Total Proteid.	Fibrin.	Serum-globulin.	Serum-albumin.
Acute pleurisy, Case 1	1023	5·123	0·016	3·002	2·114
,, ,, Case 2	1020	3·4371	0·0171	1·2406	1·1895
,, ,, Case 3	1020	5·2018	0·1088	1·76	3·330
Hydrothorax . . Average of three cases	1014	1·7748	0·0086	0·6137	1·557

Exudates, as a rule, have an acidity above 10 with decinormal soda solution, using phenol-phthalein as an indicator, transudates under 10. The difference is too slight to be relied upon. Reuss, Hofmann, and others have shown that the amounts of solids and extractives vary very slightly; it is the albuminous matters which mainly determine the variations in the specific gravity. The factors determining the amount of albumin are many. Thus, as a general rule, more albumin will be found in a pleural exudate than in a peritoneal exudate. Some observers, however, place peritoneal exudate first in order. The pericardial and the subcutaneous come next. It has been noted, further, that the specific gravity and amount of albumin are somewhat higher in right-sided pleurisies than in left (Berheim and Brunting). The amount of albumin in the blood is also a factor. Thus in anæmia or hydræmia the specific gravity of exudates is lowered. Other factors are also given; among them the not unfrequent combination of mechanical effusion — or obstruction—with active inflammation. The most important of all would appear to be the extent of irritation of the affected part. Thus, in four cases of pleurisy, Runeberg compared the amount of albumin found in the pleural fluid with that present in acute blisters produced on the patients by cantharides; the

average of the former was 5·43, of the latter 6·2 per cent; without exception, the percentage in the blister-fluid was found the higher. It may be laid down (Miller) that fluids with the specific gravity of 1018 or higher, with at least 4 per cent of albumin, are of inflammatory origin; or from 1010 to 1015, with albumin up to 3 per cent, are due to venous stasis; of less than 1010, with albumin under 1 per cent, are due to hydræmic conditions.

The Cells of the Exudate.—Much study has, of late years, been devoted to cytodiagnosis, to the diagnosis of inflammatory and other conditions by a study of the cells present in the removed fluids. It cannot, however, be said that, for our present purposes, much has been elicited beyond this, that abundant polymorphonuclears indicate an active inflammation; a preponderance of lymphocytes, either a tuberculous infection or sub-acute inflammation of other nature of some little duration, though it has also been noted that in the early stages of a tuberculous inflammation (*e.g.* in a rapidly developing tuberculous pleurisy) there may also be an abundance of polymorphonuclears.

Fibrin.—Between the amount of fibrin present in exudations and the amount of peptones there is an inverse ratio. Peptones are especially developed in connexion with suppurative inflammation; and the more an inflammation tends to be suppurative the greater is the breaking down of the fibrin, as also of fixed and wandering cells, and the more evident the production of peptones, or more correctly of albumoses, until in chronic abscess-formation of fair extent these pass into the general circulation, and are excreted and recognisable in the urine.

Into the discussion of the mode of formation of fibrin I need not enter here, intimately connected as the

subject is with the inflammatory process. The greater text-books of Physiology enter exhaustively into the matter. Suffice it to say that, as in the blood, a direct relationship is made out between the breaking down of leucocytes and the development of this substance in inflammatory exudations.

It is in connexion with inflammation affecting serous and epithelial surfaces[1] that fibrin is more clearly recognisable, forming, it may be, thick coatings of the badly named "inflammatory lymph" over the inflamed surfaces. This deposit is in all respects comparable to the formation of thrombi in the blood-vessels (124). Here, as there, the deposit occurs only when the endothelium has undergone destruction and the roughened sub-endothelial tissues are exposed. And here also the fibrin may be deposited either in filamentous or homogeneous and hyaline form according to circumstances. How far the blood-platelets are involved in the production of inflammatory fibrin is a matter deserving further study.

The above statement gives the general consensus of opinion among pathologists of the present time regarding the mode of origin of inflammatory fibrin. And yet this view has been vigorously opposed by Neumann (125), at least as regards pseudo-membranous inflammation. According to him, careful examination of fibrinous inflammation of the serosa and of diphtheritic inflammation of the mucous membranes shows that the deposit of fibrin does not lie upon, but under, the endothelium or epithelium. The statements of other observers (Marchand, Orth, Ziegler (126)) that endothelial cells can be seen here and there still remaining under the fibrin, he strongly controverts; the cells so seen

[1] Of epithelial surfaces, more especially those covered by a single cell layer, as notably the pulmonary alveoli.

are, he declares, swollen connective-tissue cells, and the hyaline glistening bands of fibrin are seen to be directly continuous with the connective-tissue fibrils; the bands of fibrin, in short, are derived from, and are a modification of, the swollen and altered connective-tissue fibrillæ. This change Neumann terms "fibrinoid degeneration" of the connective tissue. He admits that, in acute cases free from connective-tissue proliferation, the fibrin is more probably the result of exudation. Now it is quite true that there are cases in which one cannot say certainly what is the nature of the cells seen under the fibrin; yet there are other cases in which there cannot be a doubt as to their endothelial nature. As Lubarsch (64) points out, this can be proved experimentally by causing a minimal acute local peritonitis, by simply pulling out a loop of intestine, pinching it with sterile forceps, and replacing it. If the animal be killed, in thirty-six hours small spots may be found here and there, which are covered with a finely granular, scarcely visible deposit of fibrin; in such local deposits a continuous layer of endothelial cells can be made out passing well under the fibrin, which is pure exudate. Neumann's layer of endothelium covering the false membrane certainly exists in several cases, but it is clearly of secondary development. Gaylord (127), who made a full study of the subject under Orth, has shown clearly that after introducing fibrin or fibrin-forming fluids into the serous cavities, the endothelium proliferates and covers over this foreign fibrin, sometimes before any signs of organisation appear in the mass. Undoubtedly connective tissue undergoes a change in the inflammatory area; the bundles of fibrillæ swell, become more hyaline, lose their fibrillar appearance, and form more homogeneous glistening bands. But this modified connective tissue can generally be distinguished from fibrin proper

if suitably stained by employing van Gieson's stain, or thionin.

The researches of Leo Loeb (128), conducted in my laboratory, possibly throw some light upon this subject. Taking a little lobsters' blood in which coagulation has been delayed by the addition of a solution of adrenalin chloride, and placing this upon a slide, then covering this with a second slide and pulling the one slide over the other so as to exert traction, it can be seen under the microscope that the cells, arranging themselves in rows, become transformed into a system of threads, and here and there the threads can be seen passing through a cell or even through the nucleus of a cell; the cells often become spindle-shaped and may either be so drawn out that their protoplasm forms long threads, or fine fibrillar threads may be seen actually passing through several cells. Loeb produced a similar transformation into fibrils by traction upon the protoplasm of exploded cells. It is worthy of note that, during either process, the cell-granules disappear, and these fibrillæ have staining and other reactions which connect them both with fibrin and with connective tissue. Many of them, for example, stain well by Mallory's connective-tissue stain. In other words, these observations of Loeb favour the view that the conversion of the protoplasm of connective-tissue cells into fibrillæ is the result of tension and traction, *i.e.* of physical agents, and that the same is true also of the development of the threads of fibrin. If the same process be at work in both conditions, there is little wonder that it is difficult to draw a sharp line of distinction between the intra- and extra-cellular process in tissues where both are occurring at the same time.

Leaving out of account coagulation-necrosis as not occurring in direct connexion with exudates, it may be

said that similar fibrin formation is frequently recognisable in connexion with primary inflammation of parenchymatous tissues.[1]

The beneficial effects of fibrin formation in serous cavities have been rendered abundantly manifest by the increase in abdominal surgery. No one who has followed any considerable number of operations for appendicitis can have failed to remark how, in case after case, despite the intricacy of the intestinal coils and their mobility the strongly irritant matter produced by gangrene of the appendix, or oozing through perforations in it, is restricted within a relatively small space by the surrounding fibrinous adhesions which form rapidly between the intestinal loops. By this means alone the peritonitis is restricted and "regional," instead of being generalised from the onset. Even when inflammation (as in pericarditis) affects the whole extent of a serous cavity, the layer of fibrin acts as a protective coat closing the lymphatic "stomata," hindering the free absorption of the morbid material by the lymph- and blood-vessels, and filtering bacteria out of such fluid as does find its way through to the tissues beneath. It is not a little remarkable to call to mind how case after case of purulent pericarditis or purulent pleurisy may be examined in which, despite the intense suppurative disturbance in the serous cavity, the tissues at the other side of the deposit of fibrin—the myocardium or the lung tissue—show little or no tendency to abscess formation. Let there be primary abscess-formation or gangrene in the lung, and perforation of the pleura and

[1] Where there are abundant and distensible lymph-channels extensive clotting may be seen in the lymph. This is peculiarly well marked in the contagious pneumonia of cattle (contagious pleuro-pneumonia). In acute inflammation of various organs, by appropriate methods of staining, similar formations of threads of fibrin, often starting from cells as centres, may be observed in the tissue spaces.

pleurisy may supervene: generalised pleurisy, however intense, does not lead to this unless complicated by other disease. Let there be primary or metastatic abscess in the myocardium, then there may be aneurysm and rupture of the heart; yet such rupture produced by extension inwards of a purulent pericarditis is of the utmost rarity. Let there be inflammation originating in the submucosa of the intestines, as in enteric fever, and perforation may result; general peritonitis, while often due to perforation, never —so far as I can find—directly induces that event.[1] In all these cases the natural protective layer of the serous surface is removed or gravely injured at a very early stage; and the layer of fibrin, replacing the serous endothelium, forms an effective barrier. I may add that the mucin, extruded so as to form a layer over inflamed mucous surfaces, presents a similar protective action.

But here again attention should be called to the fact that, while we can thus recognise an action beneficial to the economy in the laying down of fibrin, the adaptation to the needs of the economy is very far from being perfect, and the ultimate results are even replete with danger. I know of no better example than is to be derived from a study of the great omentum in a series of cases of abdominal disturbance (130). Time and again we find that this which, with the peristaltic action of the bowels appears to be in constant movement over their surface, has become attached by fibrinous adhesions over some inflamed area, thereby acting as a plaster or pad,

[1] Where, however, there are localised pockets of pus such perforation may occur, and what I have termed "exogenous perforative ulceration" of the intestines is much commoner than is generally suspected (129). Thus in 700 autopsies in all conditions, I encountered it seventeen times. The conditions favouring the development of the condition are adhesions after general or local peritonitis: formation of a pocket of pus, or abscess, between them; tension, acting with most effect on a soft walled viscus; compression, anæmia, and malnutrition of the wall; lessened vitality; infection; ulceration; perforation.

reinforcing a weak point and, by the adhesions, preventing generalised peritoneal infection. From this aspect alone, the great omentum can only be likened to a brooding abdominal providence. But, when these adhesions organise, the omentum, now firmly attached, forms a band or bands of most dangerous import: now constricting a coil of the intestine and so causing obstruction, or kinking the bowel, or leading to internal hernia and volvulus. In short, the late results of adhesions may be very serious.

The fibrin so thrown out, while it may (1) be dissolved by the action of bacterial products, or (2) undergo complete absorption by the cells and fluids of the body with *restitutio ad integrum* of the affected areas, may also (3) form a frame-work upon which new tissue-growth occurs with replacement by organised connective tissue. This new tissue-formation in inflammation we shall discuss later.

Passing now to the ferments and ferment-like bodies present in the exudate, I may briefly state that these are not only generated and excreted by the pathogenetic bacteria present, but are liberated by the breaking down of the wandering cells. Abundant evidence of the existence of bacterial ferments capable of acting upon proteids, gelatine, sugars, etc., is supplied by the study of the growth of these microbes outside the body. No less than six such enzymes are said to be produced by the B. pyocyaneus, for it has been shown that dead cultures of this organism will liquefy gelatine, coagulate milk, and redissolve the coagulum, invert cane sugar, split up fats, and decompose proteids. That ferments also originate from the wandering cells has been demonstrated by Leber (28), who, placing pieces of copper in the anterior chamber of the eye, thereby produced a purulent collection devoid of microbes, and showed that the exudate

was capable of digesting proteid matter. In this the leucocytes do not differ from the other cells comprising the organism. There have of late years been abundant observations by Salkowski (131), Jacoby (132), Conradi (133), and many others, upon the phenomena of autolysis, or the self-digestion of liver, muscle, and in fact most tissues, in which it has been shown that without bacterial action, but by the action of their own juices, the cells are able to digest and disintegrate themselves. Only in the inflammatory exudate the conditions favouring such self-digestion would seem to be markedly augmented. Müller (134) has shown that pus has a strong digestive action upon dead tissues, and to such autolytic action is now ascribed, on what appear to be convincing grounds, the resolution of the pneumonic exudate. Flexner has recently demonstrated that autolysis also occurs among bacteria. Cultures of the micrococcus of epidemic cerebro-spinal meningitis are very short lived. A smear from such cultures thirty hours old may show abundant typical diplococci; the same cultures a few hours later may show not a single coccus. Dying they have digested themselves.

It would seem, therefore, that, more especially in pyogenetic inflammation, the removal of dead tissue cells and dead leucocytes may, to a large extent, be due to the action of the inflammatory exudation, apart from any phagocytic action on the part of living active cells; although this also comes often into play.

The bactericidal substances present in the inflammatory exudate have already been considered. We have abundant evidence that substances capable either of destroying microbes or of hindering their growth are present therein.

Summary.—To sum up what is known concerning the inflammatory exudate, it may be said—

1. That the exudate varies in amount and in character with (*a*) the nature and intensity of the irritant, (*b*) the condition of the organism, (*c*) the region of irritation.

2. That while it undoubtedly augments the nutrition of the affected region, increased nutrition at the early stage of an acute inflammatory process would not seem to be of benefit or to play any important part. At a later stage and in chronic inflammation the increased nutrition possibly aids the hyperplasia.

3. That in many cases the exudate exerts a beneficial action by flushing out the injured area. But this same flushing-out, by distributing the microbic irritants, may also be harmful to the economy.

4. That the exudate plays an important part in diluting the irritant.

5. That the development of fibrin in certain inflammatory exudates is associated with the breaking down of the wandering cells, and is of manifest benefit in so far as it circumscribes the inflamed area, and prevents the passage of morbid material outwards. Here again the action, by favouring the development of organised adhesions, may be deleterious.

6. That the exudate may possess digestive functions, causing the production of albumoses and other products of nitrogenous disintegration; the ferments being developed from the cells alone when the exudate is aseptic, from these and the microbes together when pathogenetic microbes are present.

7. That the exudate may further contain substances, generated by the cells, capable of hindering bacterial growth, and of destroying pathogenetic microbes.

III.—THE BLOOD-VESSELS

CHAPTER XVIII

THE PART PLAYED BY BLOOD-VESSELS

The study of the action and function of the leucocytes in inflammation has profoundly modified our conception of the inflammatory process. When the leucocytes were regarded as purely passive agents, and their diapedesis as purely secondary to modified conditions of the blood current and of the vascular walls, Cohnheim's hypothesis was that most generally accepted; this hypothesis regarded the changes in the vessels as of the first importance. Thus it was that for several years our attention was mainly concentrated upon the determination of the various changes of the vessel-walls, and of the mechanism whereby these changes were brought about. Nowadays less attention is directed to this side of the inflammatory process, and it may be said that during the last ten years little advance has been made in determining the mechanism of the dilatation that accompanies inflammation. The subject, indeed, is beset with difficulties. It is most difficult to observe the changes that occur in the cells forming the endothelium of the congested vessels; we are still, for instance, far from being sure whether the opinion of Arnold (135) is

correct, namely, that the leucocytes, and, it may be, a large portion of the exuded plasma, find their way out through the dilated stomata between the endothelial cells; or whether the leucocytes pass directly through these cells as one soap bubble may be passed through another. And when we come to discuss whether the inflammatory exudation be a filtration, or whether, on the other hand, it be more of the nature of an excretion, or what may be termed a selective filtration—certain components of the blood-plasma being permitted to pass through, while others are withheld—we are met with the difficulty that, of the extravasated leucocytes, a varying proportion undergo rapid destruction and dissolution. Thus, in analysing the inflammatory serum, we are not dealing simply with the extravasated fluid, but with a fluid which in addition contains proteid and other constituents derived largely from broken-down white corpuscles, and in part, it may be, from the modified cells of the inflamed area.

Though Arnold's observations upon the altered condition of the vascular endothelium in inflammation appear at first very convincing, upon further study they seem at most to indicate that with dilatation of the vessels there is an increase in the size of the spaces between the endothelial cells. They do not, however, prove that these are other than virtual spaces filled with intercellular substance; and indeed Arnold himself came eventually to the conclusion that some such substance was present. That viscid, gelatinous substances injected into the circulation may be detected passing through these stigmata is not a proof that the spaces are actual; all it proves is that the walls are weaker in these regions; it must be remembered that increased force and increased intravascular pressure are necessary to promote the passage of the injected mass along the vessels. The

passage of the mass through the walls may therefore be an "artefact."

Kolossow (136) has demonstrated that the endothelial cells of the intima of vessels are not absolutely independent units, and that they are connected one with the other by numerous fine brides or bridges of cytoplasm. Between these bridges are the stigmata; stomata—larger spaces—are not normally present between capillary endothelial cells. He holds that, normally, the cuticular portions of the cells are in apposition, but that with distension the stigmata from being potential become actual spaces, through which the migration of leucocytes and the escape of fluid may take place.

There is this further difficulty in the assumption that these are actual spaces—that in acute inflammation the exuded fluid contains a smaller quantity of proteids than does the blood-plasma. It is true, no doubt, that the stigmata are so small they may possibly act like the pores of a filter, and consequently may not permit the free passage of certain constituents of blood-plasma. To enter into the large subject of the nature of lymph would be to pass too far afield; I can here only say that taking into consideration the abundant evidence we possess of the activity of endothelial cells—influenced also, it may be, by loyalty to my old master Heidenhain—I have not become convinced by the brilliant researches of Starling that these cells have no selective activity, governing to some considerable extent the quality and the quantity of the exudate.

We have not a little evidence that these cells play an important part in the vascular phenomena of inflammation. To their power of taking up microbes and acting as phagocytes I have already referred; into their connection with the slowing of the blood-stream I shall enter later. Here I would point out that microscopically these cells

can be seen to alter during the inflammatory process; they become enlarged and project into the lumen of the smaller vessels, and in my experience this enlargement affects not only the cell-bodies, but also the nuclei, which at the same time would seem to contain more chromatin and to stain more intensely. In cases of chronic inflammation the enlargement is followed by proliferation, notably in the arterioles and capillaries,—a process which may lead to the ultimate occlusion of these small vessels. And in acute inflammation mitosis is to be seen occurring in these endothelial cells at an earlier period than in the surrounding tissues.

A further and very important process intimately connected with the proliferation of the endothelium of the capillaries is the formation of new vessels as the result of continued inflammation. It is true that Rindfleisch (137) and others have described this as being brought about by vaso-formative cells situated externally to the vessels; and that others have advanced so far as to suggest that there are cells in the newly-forming granulation-tissue which become hollowed out and gain attachment to the pre-existing capillaries in a manner wholly similar to that observable in the vascular zone of the embryo of the chick.

The search for the earliest signs of new capillaries is a matter of some difficulty. I will not peremptorily state that Rindfleisch mistook an arrangement of cells not unfrequently seen in granulation-tissue for stages in the development of new vessels. My own observations coincide with those of Arnold, Ziegler (138), and of the majority of those who have more recently studied the question, and lead me to regard the formation of new capillaries as originating from the endothelium of the vascular loops already in existence. This, I hold, must now be regarded as settled.

The first step in the process is often recognisable, in cases of pleurisy and pericarditis, in the projection of loops of pre-existing capillaries beyond the line which indicates where the serous endothelium used to be, and into the fibrinous clot now adherent to the sub-endothelial layer. Such loops are markedly distended, and "point," as it were, at right angles to the denuded surface. A similar pointing or giving way of the wall along the convex margin of the loop is also to be made out not unfrequently in newly-developed capillaries. In these there is not, as might be expected, a thinning of the endothelium along this outer margin, but certain of the cells on the contrary appear large and active. At times a small sharp protrusion of the vessel-wall can be detected in the region of pointing. This is best seen in the capillaries that are themselves but newly formed, and composed of nothing but a layer of young endothelial cells. In this layer the protrusion can be made out to be in direct continuity with the endothelial cells of the region. At first it is solid, but in the later stages it can be seen to be nucleated, and to be growing by proliferation of the endothelial cells which thus jut outwards. Even before any further change is noticeable in this projection from the capillary wall it may be seen to be united with a similar process originating from a neighbouring vascular loop. Finally, it would appear that the joined processes become hollowed out, and thus are developed into fully formed capillary loops. It seems impossible to make precise observations on the phenomena of new vascular formation in its successive stages. I can but state that these appear to be the steps of the process. By what means the new vascular projections join together to form loops we are ignorant. Metchnikoff suggests that there must be an attraction between the neighbouring projections—a chemiotaxis—leading them to

come into apposition; that chemiotaxis is a factor in the formation of new vessels has been indicated by Conneilman (24), who has pointed out that where, in keratitis, the lesion is exactly central these new vessels are seen advancing inwards all around the periphery; where the lesion is eccentric these form only on the side nearest the lesion. That they do join is very clear to those who have studied granulation-tissue, or have observed the vascular network connecting the previously separated surfaces of a wound.

A further function of the vessel-walls is to be seen in the slowing of the blood-current. It is difficult, and in fact impossible, to explain this slowing by altered diameter of the arteries and veins. The alterations observed in the diameters of the vessels of the inflamed area are such as, acting alone, would lead to increased rate of flow. Nor again is the apparent amount of exudation, and of lymph-flow from the affected part, sufficient to make it probable that (as Wharton Jones (139) first suggested) the slowing is in the main due to the concentration of the blood, relative drying of the corpuscles, and consequent increase of friction; while this may be an adjuvant we must, I think, find some more potent factor. What this factor is was pointed out long ago by Lord Lister (140), who, in 1858, noticed that coincident with the slowing of the blood-stream, the corpuscles move sluggishly along the vessel-wall as though attracted by it. He essayed to prove this by an experiment performed previously by Weber (141). He ligatured a frog's leg, then irritated a portion of the web by a little mustard, and found that, although the blood-current had ceased, there was nevertheless an accumulation of corpuscles in the vessels of the irritated area, the corpuscles gliding into the affected region and becoming adherent there. Ryneck (142) has shown that this

accumulation is not due to increased adhesiveness of the

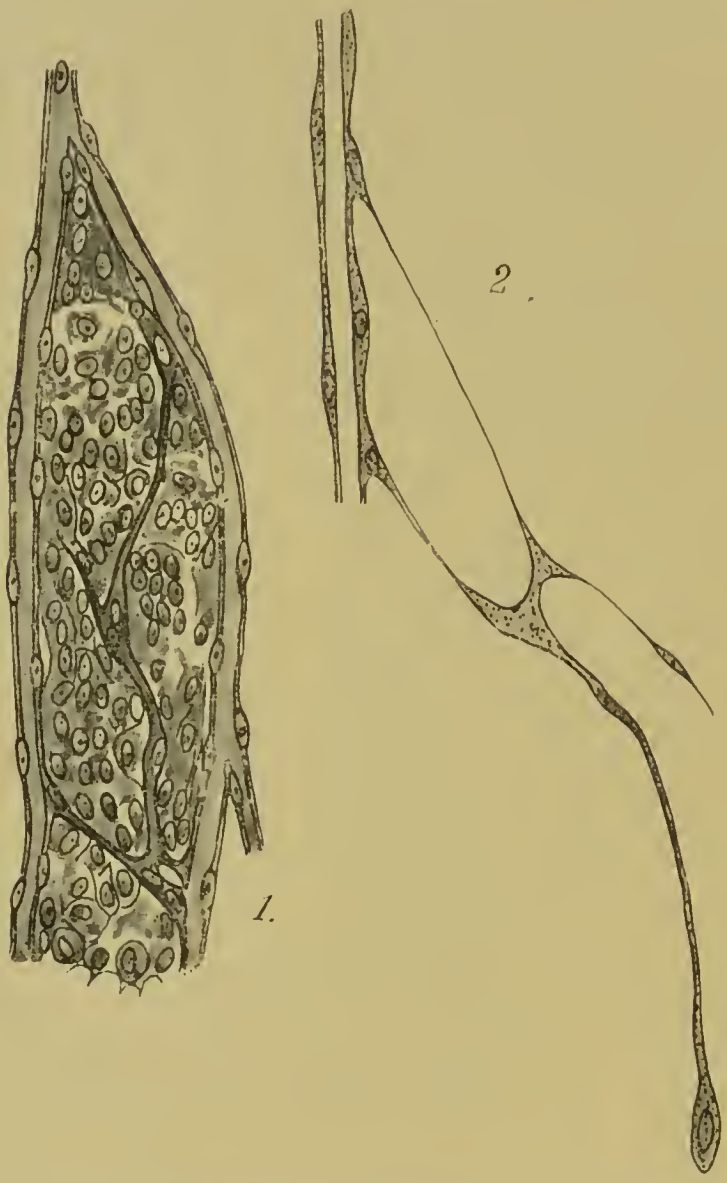

FIG. 16.—Formation of new vessels in inflammatory tissue. (1) From a Ziegler's chamber (*i.e.* one formed of two cover-slips) left in the peritoneal cavity for forty-eight days. The tissue formed between the cover-slips consists of uninucleated and multinucleated formative cells. It is bounded by fully-formed new capillaries, and in the angle between these the solid buds or processes of developing new capillaries are well seen. (2) Formative (connective tissue) cells in direct connexion with the endothelium of newly-formed capillaries. From a similar preparation.—ZIEGLER.

red corpuscles, inasmuch as similar slowing and stasis

may be induced if the blood of the frog's leg be replaced by milk and the web irritated. In this case there is a gradual slowing of the stream of milk and accumulation of the fatty globules in the inflamed area. If, on the other hand, the vascular endothelium be killed by the action of circulating metallic poisons, then he found that no stasis occurred. And in favour of these views of Lord Lister and Ryneck is the fact already noted, that in inflammation the endothelium of the vessel-walls becomes altered, the cells becoming enlarged. With this, as evidenced by the conduct of the white corpuscles, they become more adhesive, and this adhesiveness with the associated increased friction between the vascular walls and contents I regard as the first factor in bringing about the slowing of the blood-stream. Let the current once accelerated be rendered slower by this increased friction, then transudation may accentuate the accumulation of corpuscles.

Summary.—While there is very much yet to be learned concerning the part played by the blood-vessels in inflammation, and while our present knowledge of this branch of the subject can only be regarded as very imperfect, the following may, I think, safely be said to epitomise what is known at the present time :—

1. That the vascular walls, and more especially the endothelial cells lining the capillaries, play an active and not a passive part in the inflamed area.

2. These cells have the power of throwing out pseudopodia and of taking up non-motile bacteria.

3. They are larger and more prominent during inflammation than they are under conditions of health.

4. From them are developed the new vascular loops in cases of more chronic inflammation.

5. Their inner surface would seem to become more adhesive in inflammation, and by this, in the first place,

to lead to the arrest and adhesion of the leucocytes and red corpuscles.

6. Similarly they would seem to cause an increased resistance to the passage of the blood-current, and thus tend to slow the rate of blood-flow.

7. The slowing of the stream may further be aided by the passage through the walls of increased amounts of fluid from the blood.

8. It is impossible by analysis of the inflammatory exudation to determine whether this be a mere filtrate or be the result of a selective activity of the endothelium. On the whole there appears to be a combination of the two processes.

Other properties of the blood-vessels in respect of inflammation will be better discussed in later sections in connexion with the discussions of the part played by the nerves, and of the formation of new tissue.

CHAPTER XIX

ON THE PASSAGE OF CORPUSCLES OUT OF THE VESSELS

By his researches, Cohnheim (1867) forcibly attracted the attention of pathologists to the diapedesis[1] of leucocytes in inflammation—a process which had already been very clearly described years before by W. Addison (143) (1843) and Waller (144) (1846) in England; and yet earlier (though without grasp of the connexion between the diapedesis and inflammation) by Dutrochet (145) in France (1828). Cohnheim recognised the amœboid nature of the leucocytes, and saw that once outside the vessels they moved actively, but eventually he could not discover that their penetration of the vessel-walls was anything but passive, although twenty years previously Augustus Waller had clearly described the active nature of the process; and this failure on Cohnheim's part to recognise the true nature of diapedesis confirmed him yet more strongly in the view that the all-important factors in the inflammatory state were the changes in the vessel-walls, and, it may truly be said, arrested his advance towards a fuller comprehension of the subject.

[1] It has been objected that the term "diapedesis" should strictly be employed to denote only the passive transit of red corpuscles out of the vessels. If the word was originally employed in this sense it was an incorrect use: the term clearly indicates an active process—a "footing through" or jumping through.

It must be acknowledged that there is much which would seem to support this view of the passivity of the leucocytes. No one is prepared to attribute active movements to the red corpuscles, nevertheless in inflammation a certain number of these escape through the vessel-walls. In the inflammation affecting some organs, notably the lungs, the number effecting a passage is very considerable. If, then, the red corpuscles emerge passively, why should not the emergence of the white be passive also? Add to this the very important observations made by Cohnheim, that where the circulation is arrested by compression of the artery there diapedesis ceases. This, if invariably true, would seem to indicate that when once by changes in the vessel the leucocytes adhere to the wall, the further passage through that wall is due to the *vis a tergo* of the blood-pressure.

This, however, is not a safe deduction to draw from the experiment referred to. When the artery of an inflamed area is compressed the stoppage of the blood-stream not only reduces the pressure, but also affects the quality of the blood and the conditions of the vessel-walls; moreover, it must profoundly affect the vitality or at least the activity of the contained leucocytes. These considerations alone render the experiment valueless as a proof of the passive nature of the diapedesis. Again the passage outwards of red corpuscles does not occur in the earliest stages of reaction to irritation; it never precedes the diapedesis of the leucocytes (save where there is gross injury), but follows it. A capillary or small vein in the inflamed frog's web, for example, may be seen wholly filled with corpuscles, the peripheral zone being quite annihilated, and numerous red corpuscles lying in immediate contact with the walls; nevertheless at first leucocytes only emigrate. This difference must be due to some special property of these cells. The leucocytes

in the blood-stream are not necessarily globular passive agents, but are capable of independent movement. Leber (28), in his long series of studies, has pointed out that if, with due precautions, a hooked glass tube (closed at its outer end where it catches into the incision in the wall) be inserted into a large vein no thrombosis may be set up around the intravascular portion, and yet, upon removal, a large collection of leucocytes may be found in the tube, attracted by a drop of mercury placed, along with normal salt solution, within it. (Mercury is a substance which within the tissues leads to an accumulation of leucocytes.) Here, then, there must be active attraction and active movement of the leucocytes within the blood-stream. And Lavdowsky (147) has described very exactly what other observers had also noted, namely, that in inflammation the leucocytes in the outer zone of the blood-stream do not simply adhere passively to the wall, but move backwards and forwards before they attach themselves and emigrate, as though seeking for a point of less resistance. At times this movement is in a direction opposite to that of the blood-current. Further, Councilman has called attention to the suggestive fact that in the process of migration the nucleus is always directed to the objective point and, with a small surrounding of cytoplasm, is the first part of the cell to pass through the capillary wall. More than one observer has seen a relationship between the labile, broken-up character of the nucleus of polymorphonuclear leucocytes and their function of passage through minute orifices in the capillary walls.

If both within and without the vessels the leucocytes can be actively amœboid, it is strange that they should be passive in the process of diapedesis which to the eye has so characteristically amœboid an appearance.

As above stated, the compression of the artery passing to an inflamed area is in most cases sufficient to arrest

diapedesis in that area, and I have suggested that this arrest may be due to the altered environment of the leucocytes. Now, if an embryonic form be taken, in which the tissues would seem to possess greater inherent vitality coupled with less sensibility, the arrest does not necessarily occur. Thus, Metchnikoff has noted that diapedesis of the leucocytes can be followed in the tadpole's tail, after the animal has been curarised to such an extent that the heart has ceased to beat and the blood in the capillaries has been brought to a standstill.

It is evident, therefore, that with our present knowledge we must regard the diapedesis of the leucocytes as an active migration, and must look upon the blood-pressure, the disposition of the blood-stream, and the altered condition of the endothelium of the dilated vessels as adjuvants in the process. The slowing of the blood-stream and the diminished pressure in the inflamed capillaries render it more easy for the leucocytes to accumulate close to the vessel-wall; the dilatation of the vessels and consequent thinning of the walls, with the opening, perhaps, of larger spaces of cement substance or stigmata between the individual endothelial cells, render it more easy for the leucocytes to accomplish the passage; but the movement from within the capillaries to the tissue-spaces outside is an active process due to amœboid movement of the leucocytes themselves. The continuity of the vessel-wall once destroyed, other cells — red corpuscles—may be pressed passively through the walls.

If this view be accepted, we are bound to look beyond Cohnheim's limit of changes in the vessel-wall for the stimulus which, originating in the area of irritation, acts upon the vessel-wall and the leucocytes in contact with it, and, having first set up changes in the former, so reacts upon the latter that they emigrate; or, to put it in other words, are attracted out of the capillaries

towards the focus of irritation. It has already been shown that the movement of wandering cells in the tissue is due to the attraction of a diffusible product of

FIG. 17.—1. Capillary (inflamed) of frog seen in profile, exhibiting margination of leucocytes, assumption of pear-shaped form, and migration through wall; a leucocyte adherent by long process. 2. Leucocytes in process of diapedesis, showing the pseudopodia on the outer aspect of capillary. From mesentery of rabbit, also in profile: higher magnification.—LAVDOWSKY.

bacterial growth and of tissue change, and of sundry organic and inorganic materials—the force to which the name of positive chemiotaxis has been given. Chemiotaxis must be invoked to explain the active emigration of the leucocytes from the capillaries, and

again to explain its cessation under other conditions. Thus, while the exposed mesentery of a frog is a tissue in which diapedesis can be observed with facility under ordinary conditions, if it be washed with a weak solution of quinine, the leucocytes in the vessels remain globular, cease to adhere to the walls, and do not emigrate. This observation, first noted by Binz (148), has been confirmed by others, among whom Disselhorst (149) made out also that, if these same leucocytes be removed from the vessels, they exhibit their usual amœboid movements. The quinine has not paralysed them, as Binz supposed; but, as Metchnikoff pointed out, it has neutralised the previous positive attraction, a negative or repulsive chemiotaxis being brought into play. It is difficult to see how these observations can be otherwise explained.

The view that diapedesis is an active process gains further support from, and at the same time explains certain interesting observations made by Bouchard (150), Roger (151), Charrin (152), and Ruffer. These observers have independently shown that in sundry instances the results of local injection of virulent cultures are greatly modified if, shortly before or coincidently, the microbes and their products are introduced into the circulation. Thus, as Ruffer points out (153), a drop of the culture of the bacillus pyocyaneus inoculated into the anterior chamber of the rabbit's eye leads ordinarily to a great migration of leucocytes—to an acute purulent inflammation. If, however, the toxins produced by this microbe have previously been injected into the circulating blood, no accumulation of leucocytes follows inoculation into the eye. Ruffer also extended most suggestively certain observations of Roger (151). Subcutaneous or intramuscular inoculation of the rabbit with the bacillus of symptomatic anthrax leads to the production of a local abscess with extensive accumulation of leucocytes. After

simultaneous injections of fluid containing virulent bacilli and their products into the vein of the ear and the muscles of the hind leg, Ruffer found the rabbit dead, within fifteen hours, with a huge tumour in the inoculated limb. Here, upon examination, the muscle-fibres were found widely separated by fluid exudate, in which there had been great multiplication of the bacilli; but leucocytes were entirely absent. In these two cases we have therefore diapedesis and determination of leucocytes following the purely local action of the toxin; want of diapedesis and absence of leucocytes when the toxin at the same time circulates in the blood-stream. Wholly in line with these are the observations of Sidler (154). Solution of iodine, injected subcutaneously into the ear of a rabbit, sets up an inflammation characterised by extensive exudation with associated abundant migration of leucocytes into the part. With the injection of 0·05 per cent iodine solution peripherally into the ear vein there is the same or even more extensive fluid exudate, but no leucocytosis. If any large proportion of the leucocytes which find their way to a focus of irritation emerge from the blood-stream, these divergent results are only to be explained by some hypothesis which is capable of reconciling the difference in the action of the leucocytes when they are circulating in normal and in toxin- or irritant-containing blood respectively.

Now, the results in these cases are entirely consonant with what we know concerning the sensitiveness and reaction to stimuli not only of unicellular organisms, but also of the higher animals. Organisms, whether lowly or of most complex development, only perceive and react to alteration in their environment when the alteration exceeds a definite ratio. Thus, as Pfeiffer has pointed out, a motile bacterium (the "B. termo") is attracted towards solutions of peptone; if it be already

in a peptone solution, in order for it to be attracted towards and move into a more concentrated solution, this last must be five times as strong as is the former. This is in conformity with the psychophysical law of Weber-Fechner: that sensibility increases in arithmetical ratio when the stimulus or excitation increases in geometrical ratio—or, in other words, reaction is in proportion to the logarithm of the excitation. The only possible explanation that I can see of the above observations of Ruffer, Roger, and Sidler is that the passage and want of passage of the leucocytes out of the vessels depends upon the ratio of diffusible bacterial products present in the blood-stream and in the tissues respectively. Where the products are localised at one focus in the tissues, the leucocytes are attracted out of the unaltered blood, and there is active diapedesis; where there was already a solution of the bacterial products in the blood, the ratio of difference between the percentage amount of toxin in blood and tissue may be insufficient to stimulate the leucocytes; no diapedesis then ensues.

As is well shown in the experiment with symptomatic anthrax, the presence of the bacillus and its products in the circulating blood did not prevent inflammation at the region of local injection; inflammation and exudation were abundantly manifest—there was, in fact, a more extensive exudation than ever. The irritant—that is to say, the toxic products of the bacilli—at the point of injection was in no wise hindered from exerting effects upon the fixed cells of the vessel-walls, and promoting all the changes in calibre and condition of the walls and in the blood-stream characteristic of inflammation. But with vascular changes, if anything more prominent than in the case where local inoculation alone had been practised, the leucocytes stayed within the vessels. Now the only cause to which we can attribute this abstention of the

cells from emigration is lack of attraction—certainly not lack of vascular change or lack of blood-pressure.

Summary.—We are thus led to the following conclusions regarding the passage of cells out of the blood-stream into an inflamed area:—

1. The diapedesis of the leucocytes is, as the name implies, an active and not a passive process; it is due to active amœboid movements on the part of the cells.

2. The stimulus leading to diapedesis is that of positive chemiotaxis. It is the attraction exerted upon the leucocytes by the diffusible substances associated with the irritant.

3. Irritants, if themselves diffusible, or the diffusive substances developed while the irritants are within the tissues, are capable of two separate actions: one direct upon the vessel-walls, leading to vascular changes; the other through the walls upon the leucocytes, whereby emigration may be induced.

4. These two actions need not (and frequently do not) manifest themselves *pari passu*.

5. In relation to diapedesis, the dilatation of the vessels, the altered rate of blood-stream, the altered disposal of the corpuscles in the stream, and the modified endothelium, may all be regarded as adjuvants.

6. The passage of red blood corpuscles from the blood-vessels into the inflamed area is passive, due to the blood-pressure and to lack of continuity of the vessel-walls. Such lack of continuity is favoured in many instances by the migration of the leucocytes through the walls.

IV.—THE NERVOUS SYSTEM

CHAPTER XX

ON THE PART PLAYED BY THE NERVOUS SYSTEM

If the vascular changes in inflammation were due to reflex influences proceeding from the central nervous system, and were in fact controlled by the centres in the brain and spinal cord (as has been held by the supporters of neuro-humoral hypotheses), then, in the first place, there should be a rapid and almost immediate response on the part of the vessels of any region on the introduction of an irritant. But this is not by any means constantly observed. Thus, as Cohnheim pointed out, if croton oil be rubbed upon a rabbit's ear, more than an hour may elapse before the first beginnings of hyperæmia can be detected; yet the inflammation eventually set up may be very intense. In the second place, section of all the nerves passing to any region of the body should have this effect, that injury in the region in question should be unaccompanied by the ordinary vascular reaction. But this is not the case. Divide all the nerves which supply a rabbit's ear, for example, and then injure that ear, either by heat, cold, or inoculation of pathogenetic micro-organisms, and inflammation manifests itself with all the stages recognisable in an ear with intact nerve-supply. The vascular changes which accompany inflammation can

occur then independently of any central nervous influences.

We can proceed further, and state that regions deprived of their nerve-supply are peculiarly prone to inflammatory changes. But this liability to inflammatory disturbances in such regions is not directly due to the destruction of vasomotor tracts and the cutting off of central influences from the vessels of the part, but is, it would seem, immediately connected with the loss of sensation. Divide the ocular branch of the fifth nerve of a rabbit, and, if the eye be not protected, ulceration and necrosis of the cornea manifest themselves in the course of a few days. Protect the eye, either by bringing the lids together or by placing a shade over it in such a way that dust and foreign particles are prevented from settling upon the surface, and no such ulcerative disturbance manifests itself. From this it is clear that the primary cause of the inflammation is not any trophic change in the region, but is the lack of sensation, whereby irritant substances are permitted to gain a lodgment upon the outer surface without any attempt being made to remove them. That, in addition, there is a lowered vitality in parts deprived of their nerve-supply, and that this renders those parts a more favourable seat for inflammatory disturbances is more than probable; nevertheless, this would not seem to be the primary cause of the increased liability to inflammation.

This, then, in the first place, is clearly recognisable—that the vascular changes accompanying inflammation can occur independently of central nervous influences. Hence it follows that there must be a *peripheral* mechanism controlling the vessels. It remains, therefore, to determine the nature of this peripheral mechanism: is it wholly under the guidance of peripheral nerve-cells situated in the vessel walls, or is it, in part at least, idiocellular? In the present state of our knowledge the

answer to this question must be guarded. The more carefully the innervation of the various regions is studied, the more clearly is it demonstrated that throughout all the tissues of the body there exists a wonderfully fine and complicated network of nerve-filaments with occasional isolated ganglion-cells. Yet proof is wanting that this system in connexion with the vessels is sensorimotor. Indeed, so far as regards the heart and ventricular muscle (which may be looked upon as the region of the vascular system wherein the motile portion of the walls has become specially developed), the researches of Romberg and His lead rather to the conclusion that the peripheral nervous system subserves sensation alone. Nevertheless, there are observations to the contrary. Mall (155), for instance, has demonstrated the existence of motor nerves in the portal vein, finding that after ligature of the thoracic aorta stimulation of the splanchnics causes the portal vein to contract until the lumen almost disappears. The portal vein, it is true, has functions differing from those of most other veins; but this observation renders it possible that some veins, at least, may be modified by central stimuli in the course of the inflammatory process.

At the same time, the more the activity of the various tissues is studied, the more fully it is seen that many cells retain what may be termed reminiscences of an earlier and more embryonic condition in which their functions were varied and less specialised. There is an inherent probability that the endothelial cells can react directly to stimuli, and that they are capable of idiopathic contraction and expansion on appropriate stimuli. We have seen that these cells are capable of taking up microbes, and thus obviously exhibit an independent activity similar to that observed in the amœba or the wandering phagocyte. If these cells, then, are capable of throwing out pseudopodia, and thus of enclosing non-

motile bacteria, are they not capable of contracting and expanding, as a whole, according to the stimulus of altered environment? As a matter of fact, such contractility of the endothelial walls of the capillaries has been demonstrated by Klebs (156) and Severini (157). I cannot but conclude, then, that at least the endothelium of the capillaries is to some extent self-regulative or neuro-muscular. It is quite possible that the muscular coats of the smaller arteries are likewise capable of self-regulation, and respond directly to stimuli. In their recent studies on the sympathetic innervation of the rabbit's ear Dr. and Miss Meltzer (162) have demonstrated that after section of all the sympathetic fibres to the ear, the resultant hyperæmia disappears in some days, the vessels contracting, and this before any signs of nerve-regeneration can be detected. In other words, the arteries regain their tonicity without the aid of extrinsic nervous influence. That inflammatory dilatation of the vessels differs from simple vasomotor dilatation they demonstrate by the action of adrenalin: this is followed by rapid contraction in the latter condition, but is without effect in the former. The continuance of pulsation in the veins of the bat's wing when the nerves have been cut through, suggests either that the muscle of the walls has independent action or the existence of local ganglionic centres.

There is, indeed, something characteristic about the inflammatory dilatation of vessels — something not observed in other conditions—in active arterial hyperæmia or in venous obstruction. As Samuel (117) points out, if intense venous obstruction of the rabbit's ear be produced, the larger vessels are seen greatly engorged; but puncture of the skin outside the visible vessels, or even of the ear with a fine needle in such a position, is not followed by the escape of even a drop of blood—

the capillaries remaining contracted. Puncture outside the visible vessels in the inflamed ear and the outpouring of blood is quite extensive. There is, in short, an active dilatation of the capillaries.

This view—that the vascular phenomena of inflammation can occur independently of the central nervous system and of the peripheral nerves—does not imply that the nervous system, central and peripheral, is without its influence upon the process; far from it. We have evidence, in the first place, that the state of the vascular walls is modified after destruction or severance of the nerves. I do not here refer only to the consequent alterations in calibre of the vessels, but also to the changes in other properties. Thus Gergens (158), and to a less extent Rütimeyer (159), noticed that after destruction of the spinal cord the blood-vessels of the frog permit a larger quantity of fluid, and even particles of granular colouring matter, to permeate them.

In the second place, we have evidence that the central nervous system exercises some direct influence upon the inflammatory process. From Cohnheim onwards it has been a matter of common observation that when all the nerves of a part have been severed, the stages of the process succeed each other with greater rapidity. It may be that the modified state of the capillary walls, noted in the preceding paragraph, is capable of accounting for this fact, and that, in the absence of central influences, dilatation of the vessels and exudation of fluid lead to the cardinal symptoms of redness and swelling, with associated changes in the tissue, at an earlier period.

Of the part played by the different sets of nerves the external ear of the rabbit again furnishes an excellent study. This part has a double nerve-supply through

the auriculars (major and minor) from the cervical plexus and the sympathetic branches from the superior cervical ganglion: stimulation of the former leads to dilatation of the ear vessels (vaso-dilator action), of the latter to contraction of the same (vaso-constrictor). If, as shown by Samuel (160), the sympathetics be divided on the one side, and the auricular branches upon the other, the ear vessels of the former side become widely dilated (unimpeded action of vaso-dilators), and those of the latter markedly constricted. Under these conditions, if both ears be subjected to the action of water warmed to 54° C. there is a characteristic difference in their reaction. In the organ deprived of sympathetic influence the congestion and hyperæmia become yet more pronounced: an acute inflammation sets in which proceeds rapidly to recovery. In the opposite ear, with its constricted vessels, no hyperæmia is set up; but there is stasis, and gangrene may supervene. These results have been confirmed by Roger (161), who, taking a rabbit and dividing the sympathetic on one side, and then inoculating both ears with like quantities of a culture of the streptococcus of erysipelas, found that the erysipelatous process manifested itself much more promptly upon the paralysed side, and came to an end at an earlier date. The reverse was the case when the auriculars of the one side had been divided: here the process was of slower development than on the intact side, and of slower course, resulting in mutilation of the organ. Further confirmation is afforded by the researches of Meltzer and Meltzer (162).

The inference to be drawn from these observations is that section of all the nerves passing to the rabbit's ear permits the inflammatory process to run a more rapid course; section of the sympathetics (vaso-constrictors) alone has the same effect; while the uncontrolled action

of the sympathetics after section of the auriculars (vaso-dilators) hinders or prevents the manifestation of the ordinary processes of inflammation, and by preventing the destruction or removal of irritant matter favours necrosis of the tissues. We have yet to learn whether these results are capable of a general application, and to discover how far they are borne out by clinical observations on diverse cases of localised paralysis. So far as they go they afford direct evidence of the power of the central nervous system to modify the course of the inflammatory process, while they demonstrate admirably how potent an auxiliary is the dilatation of the vessels in the inflammatory process.

Other evidence that the state of the nerve-supply of a region influences the manifestation of inflammation is afforded in sundry neuropathies. In all of these, in the present state of our knowledge, it is difficult to trace out the nervous factors associated with the lesions to which I refer. Our knowledge of the respective influences of trophic and vasomotor nerves is far too limited to permit us to say more than that a relation exists between the condition of the nerve-supply of the affected area and the inflammatory lesions there observable; that in a certain number of cases inflammation affecting the area supplied by one branch of a nerve may have associated with it definite inflammatory disturbances in the areas supplied by other branches of the same nerve, and that, similarly, when inflammation affects a viscus, inflammatory phenomena may be sympathetically developed in regions innervated from the same area in the brain or spinal cord. I have already given examples in support of the first statement: the familiar redness, swelling, heat, and pain of the side of the face which may accompany toothache is an example in support of the second. Head and Campbell's thorough studies upon Herpes zoster (163) show that lesions

affecting the nerve centres—in this case the posterior root-ganglia—may be the main factor in the development of an intense inflammatory process in the areas governed by those centres—a process so far unassociated with the presence of bacteria, although the appearances suggest infection. Another example is to be found in the acute nephritis which at times rapidly follows the passage of a catheter or the impaction of a stone in the urethra. It is not unlikely that many of these sympathetic inflammations are not direct, but secondary. Thus, the first noticeable symptom of catheter fever is suppression of the urine. Such suppression might be brought about either by reflex contraction of the renal arteries, or, contrariwise, by reflex great dilatation and congestion of the vessels of the kidneys. If it be caused by the former then the nephritis can only be regarded as secondary, and as due to the injury done to the organ by the stoppage of its blood-supply for some little time. Undoubtedly in many cases of catheter fever the nephritis is infective, but in some the condition supervenes so rapidly that it is difficult to believe that we have to deal with an ascending infection. Where there is infection it develops in such a way that we are led to see that the altered condition of the organ under various influences has favoured the inflammatory process.

From the multitude of the factors involved, these examples, taken separately, afford at most only a great probability that the nervous system can directly originate inflammatory changes. There is, however, the clearest proof that the nervous system does possess this power, and this is afforded by the results of certain observations upon hypnotic effects. In some persons susceptible to hypnotic suggestion, the suggestion that a red-hot substance has been placed upon the hand will, in the course of a few minutes, lead to great reddening of the

part supposed to have been burned, and this reddening may be followed by great local exudation and swelling—in fact, by all the symptoms of acute inflammation, save this, that the exudation is simply serous, not passing on to anything approaching pus formation, *i.e.* the migration of leucocytes would seem to be wanting. Here then actual inflammatory reaction follows supposed injury. Characteristically there is a tendency for the lesion to be bilateral, "reflected" upon the corresponding region of the other side of the body.

It is unnecessary to do more than point out the light that this intervention of the central nervous system throws upon the subject of counter-irritation, and upon the modifications of the course of inflammations brought about by idiosyncrasy of the individual.

From what has been said in the preceding paragraphs it follows that:—

1. Acute inflammation in all its stages may proceed regularly in the absence of all centrifugal nervous influences.

2. The vessels of an injured area are capable of reacting apart from central influences: it may be either directly, or under the control of a peripheral system of nerve-cells.

3. The central nervous system is capable of modifying the process of inflammation. It would appear that when the vaso-dilators alone are called into action the successive stages of the process are accelerated. When the vaso-constrictors alone are acting the process is retarded.

4. Centrifugal impulses alone, apart from any local injury, may originate a succession of phenomena of inflammation in a part.

5. Hence, in all probability, a nervous and central origin must be ascribed to some, at least, of the

sympathetic inflammations seen to occur in areas supplied by the other branches of a nerve supplying a part primarily inflamed; and again in areas supplied from the same region of the brain or cord as the inflamed organ.

V.—THE CELLS OF THE TISSUES

CHAPTER XXI

DEGENERATIVE PROCESSES

As a consequence of irritation two opposed processes may be manifested in the cells of the affected area,—changes leading to impairment and death, and changes leading to overgrowth and proliferation; degeneration and regeneration.

Either of these two processes may, it is true, be wholly wanting. In very acute suppurative disturbances, destruction of the tissue-cells and the steps leading to destruction may be the only recognisable changes. Again, in the first stage of most injuries, whether of mechanical, chemical, or bacterial nature, degenerative changes are wont to take the lead. On the other hand, there are irritants so mild that little or no cell-destruction results from their action; an extreme example of this category of inflammations is seen in those epithelial overgrowths commonly known as "corns," due, as Sir James Paget pointed out in his lectures, to intermittent pressure and irritation of moderate intensity.[1] Other

[1] It may very well be that this is not an extreme example. Neoplasms as a class, whether malignant or benign, not improbably develop as a consequence of some irritation having an intensity just sufficient to induce

examples are to be found in the "catarrhal" inflammations, in which there is marked initial overgrowth and proliferation of the cells of mucous membranes; and in tuberculosis, again, in which characteristically the earliest effects upon the pre-existing cells, produced by the presence and growth of the tubercle bacilli, are those of enlargement and multiplication—necrotic changes, as a rule, only appearing at a much later stage. Once more, in the later healing stages of injuries, cell-proliferation may be in the field alone. Nevertheless, in a very great number, if not in the majority, of inflammations, the two processes may be found occurring together—destruction and degeneration being in evidence at the focus of irritation, and growth and proliferation towards the boundary zone, where the irritant is acting in a less concentrated form.

Although the two processes are thus so frequently associated, it will be well, for the orderly review of our subject, to consider them separately.

Degenerative Changes.—Death of the pre-existing cells as an immediate consequence of injury cannot be regarded as one of the phenomena of the inflammatory process. Immediate death of the cells may be a result of injury, and the disintegration of the dead cells may in itself lead the way to all the symptoms of inflammation.

cell-proliferation, and continued for a time sufficiently long to impress upon the cells of the affected tissues the habit of rapid multiplication. There is evidence both in animal and vegetable pathology favouring this relationship between inflammation and neoplastic growth. The objection may be raised, with considerable force, that substances which lead to cell-proliferation are stimuli and not irritants, and that a line should be drawn between inflammation proper and overgrowth the result of irritation. I, for one, would willingly make this difference, but while it is easy to draw the line in certain well-marked examples, in others, as I shall proceed to show, cellular proliferation is so essential a part of the whole inflammatory process that the division becomes impossible.

But cessation of action is not reaction, nor is failure response, and throughout this study inflammation has been considered as the reaction following injury, and the response to it. Thus immediate death of tissue-cells is resultant and not reactive, and may be eliminated from the category of the essential phenomena of inflammation.

The same is to some extent true of cell-degeneration, but not entirely. While it is impossible now to accept Virchow's view, that inflammation is essentially a process characterised by increased nutritive changes in the cells of the tissues (164), it remains most probable that in very many cases irritation induces increased, even if perverted, activity of certain orders of cells. The proliferation, swelling, and more or less rapid degeneration of these cells cannot be wholly ascribed to the toxic influence of the irritant, but must in part be regarded as a result of over-stimulation and overwork. This is most noticeable in connexion with catarrhal and parenchymatous inflammations. In parenchymatous nephritis, for example, such as that set up by cantharidin or infection, the cells especially affected are those whose functions are especially excretory; and their degeneration would appear to be intimately related to the performance of their functions. Such degeneration, preceded or accompanied, as it so frequently is, by excessive proliferation, may truly be regarded as reactive, and not as wholly and primarily destructive.

Of the degenerations which affect the tissue-cells (and often at the same time the leucocytes) in inflammation there are many varieties; in fact, according to the nature of the irritant, one, or other, or all the degenerations affecting the tissues in different pathological conditions may manifest themselves, save, perhaps, simple atrophy and pigmental degeneration (as apart from pigmental infiltration). Most commonly recognised are cloudy

and fatty changes, but mucoid and hydropic changes are far more frequent than is generally noted. Even so specialised a change as amyloid degeneration has been observed occurring locally in chronic inflammations—as, for example, in gummas; while in these same chronic lesions hyaline degeneration in the vessel-walls is very frequent.

There is a further form of degeneration met with in inflammatory disturbances which deserves more recognition than it has generally received. This is what may be termed *reversionary metamorphosis*. To speak of it as reversionary degeneration is, perhaps, a misnomer, although, if the irritation be continued, the modified cells undergo atrophy and destruction. It is not seen in acute inflammations, but in more chronic cases. As I have pointed out elsewhere, functional activity and active growth and multiplication of the cells of the organism are largely incompatible. The performance of function necessitates katabolism and breaking down; growth demands a building-up and increase of the cellular bioplasm. Thus, in the course of active cell-multiplication, the individual units lose, to a certain extent, the finely differential histological features associated with the performance of special function, and revert to a simpler, more embryonic type. All inflammatory new growth, when active, presents, indeed, a reversionary character, the cells assuming appearances resembling those seen in the process of fœtal development. Even in the simplest of all tissues, namely, white fibrous connective tissue, this is to be observed. But, in some instances, it is peculiarly well marked. Muscle-fibres, for example, are developed from sarcoblasts—large cells, without a sign of striation but with abundant cytoplasm, tending to become multinucleated. In subacute inflammations affecting a muscle, the striation disappears, the

nuclei multiply, and, from the common multinucleated mass, there may be budded off or separated, isolated cells resembling hyaline leucocytes with abundant cytoplasm; resembling, in fact, the embryonic sarcoblasts. The embryonic liver shows no differentiation between liver-cells and bile-duct; both are developed from indifferent strands of cells. In the process of development those destined to be liver-cells enlarge, become polygonal, and gain abundant cytoplasm; those destined to become bile-ducts remain small, multiply, and become arranged as an epithelium. Now, in chronic interstitial hepatitis (portal cirrhosis) of the progressive type, we at times surely recognise at the outer border of the affected lobules that the liver-cells become smaller and smaller. Their nuclei also are small, and they have little surrounding cytoplasm; they form into little worm-like strands of cells isolated by the newly formed connective tissue; here and there such strands can be followed in direct continuity with the more normal liver-cells of the lobule. These are not true bile-ducts, as they are sometimes mistakenly called: the cells are irregularly arranged and do not form a true epithelium; they are more of a reversion to the indifferent stage.[1]

All these degenerations are inevitably associated with disturbance of the functions of the affected cells, and lead to their death if the irritation which has induced them be continued. But death is not the final stage to be considered. The ultimate fate of the necrosed cells varies according to the situation of the inflamed area, the intensity of the irritation, and the

[1] While these appearances can be made out in progressive cirrhosis, it should be noted that, in cirrhotic livers showing reactive hypertrophy, another condition giving somewhat the same general appearance is to be detected, namely, active budding and new formation of liver parenchyma proceeding from the bile-ducts (165). This is a process of another order, one of ascent, not of descent.

specific character of the irritant. From a free surface the dead material may be freely cast off. In acute suppurative inflammations, whether superficial or deep, and, in general, wherever there is an abundant determination of leucocytes, there obtains a digestion and solution of the necrosed cells; and, as I have already pointed out, this is associated with the liberation of many ferments, the development of peptones, albumoses, fatty acids, and other bodies, and is brought about largely through the extracellular action of the leucocytes and processes of autolysis. When there is a large area of cell-destruction, with well-developed encystment and limitation of necrosis by granulation-tissue, the solution of the dead material and subsequent absorption may be incomplete, and a fatty debris left behind, which may eventually become infiltrated with lime salts (calcareous infiltration, in the production of which, as Klotz (120) has recently demonstrated, the conversion of fatty acids into soluble soaps plays an important part). In tuberculosis, despite the presence of many leucocytes in the immediate vicinity, the dead material of the centre of the tubercle undergoes very little absorption, but remains as an inspissated, cheesy, and, later, calcareous mass. In syphilis, on the other hand, in large gummas, while there is similar death of the central cells and absence of removal, fatty metamorphosis does not occur nearly to the same extent, nor is there the same tendency towards calcification.

Lastly, although very little is known about the subject, it must be pointed out that along with the tissue-cells the intercellular matrix undergoes modifications or degenerative changes during inflammation. Among these, in all probability, is to be classed an increase in the amount of intercellular mucin, a mucoid degeneration. The inflammatory exudate is in many

cases rich in mucin, and although our knowledge of the changes in the matrix is scanty, the fact that the tissue-cells in general show little evidence of storage of mucoid or mucinogenous material, renders it probable that what mucin is formed is either excreted or elaborated between the cells. Connective-tissue fibrils, as part of the matrix, become swollen and fused into hyaline bands or masses, in which the individual fibrillæ are no longer distinguishable: in acute inflammation the next stage is the dissolution and disappearance of this collagenous matter. In chronic disturbances they are especially prone to hyaline change.

CHAPTER XXII

REGENERATIVE CHANGES

In the lower animals, as we know, injury and actual removal even of a large portion of the body may be followed by the complete reproduction of the lost part. In man, however, this reproduction of lost tissue is reduced to its lowest point; the higher the tissue the less, and the less perfect, the reproduction. Speaking generally, the tissues which show the greatest potentiality for reproduction are the least highly organised—those composed of similar units. The "connective tissue"—the lowest and most widely distributed—retains the largest powers of proliferation and hyperplasia.

In ordinary inflammation, hypertrophy and hyperplasia[1] of the connective-tissue cells are absent at the focus of irritation. Here degeneration is predominant. It is in the peripheral zone, away from the maximum concentration of the irritant, that (as shown in case after case of Leber's long series of studies upon injury to the cornea) the connective-tissue cells show signs of enlargement and proliferation, that they become more swollen and prominent, send out large processes, and may exhibit signs of active mitosis. It may be urged that this

[1] By hypertrophy in the strict pathological sense is indicated increase in *size* of the individual elements of a tissue, by hyperplasia increase in the *number* of these elements.

peripheral change is not inflammatory, but associated; yet, as I have already hinted, the signs of cellular regeneration may manifest themselves at so early a stage that it is impossible to disconnect them from the process of inflammation. This has been brought out with emphasis in Ranvier's interesting series of studies on irritation of the peritoneum by weak solutions of caustic substances, to which reference has already been made (p. 68). With abundant fibrinous exudate, engorgement of the vessels of the serous coat, presence of polymorphonuclear cells, and other signs of active inflammation, there is active direct, followed by mitotic division of the endothelial cells, some of which become enormous—100 μ and more in diameter. These cells send out processes, and take, some of them, an active part in the formation of adhesions. This is agreed, though the exact part is still a matter of controversy, whether (von Brunn (57)) they merely afford the endothelial layer covering the newly organised adhesions, or actually in part develop into fibroblasts. Here the main point is that during active inflammation cells of endothelial type are often to be seen in a state of active enlargement and multiplication.

As Baumgarten (166) showed in his studies upon the development of tubercles, in the irritation set up by the growth of the B. tuberculosis in the tissue, a like overgrowth with proliferation of the fixed cells occurs in the immediate neighbourhood of the bacilli without any primary evidence of cell-degeneration. It is true that the researches of Borrel (72) have thrown doubt upon Baumgarten's observations, but they confirm the earlier researches so far as regards the mitosis of pre-existing cells, and the absence of degeneration of these in the earlier stages of the tubercular growth. Borrel would regard all the large epithelioid cells of the tubercle as modified leucocytes. If we assume, as I think we must,

that cells of the hyaline mononuclear type have a common origin, whether passing to the part from the blood or developing from pre-existing cells of the part—that hyaline mononuclear cells are derived from endothelial cells in the main—we then harmonise, or find a *via media* between, these opposing views.

It deserves mention that Virchow's teaching that cells may undergo growth as a consequence of the inflammatory reaction, was vigorously opposed by Carl Weigert (167), according to whom cell growth and formative, as distinguished from functional processes, were an intrinsic inherent property of living matter, a property that could not be stimulated by chemical and other influences acting from without, though it could be hindered in its manifestations by mechanical influences such as the pressure of surrounding cells. What Virchow had adduced as examples of cell growth he regarded as evidences of cell degeneration. Weigert's views have exercised a profound influence upon the pathology of the past generation. They do not, however, express the whole truth and are untenable. He neglected to take into account in his reasoning on this matter the possibility that increased functional activity on the part of the cell, initiated from without, might under certain conditions not merely result in heightened katabolism, but that in this process of katabolism the products of dissociation of the cell substance might attract other matter to the cell, and so favour a coincident and even greater assimilation, leading to increase in the amount of cell substance. Certain it is that of late abundant instances have been brought together by Levin (168) and others which can only be interpreted on the view that a certain grade of stimulation or irritation favours cell growth, and a higher grade cell disintegration—the position, I may add, upheld in the first edition of this study. Physiologists are now afford-

ing abundant instances to the point, demonstrating, for example, that the internal secretion of the thyroid directly stimulates growth, and that the growth of the mammary glands during pregnancy is not of nervous origin, or in any way connected with nervous control, but is due directly to the influence of substances diffused into the maternal blood from the growing fœtus during pregnancy. Professor Starling (169) in describing his series of experiments affords a useful resumé of cognate examples.

The difficulty of determining the origin of the growing cells in inflammation has formed the greatest trial of the pathologist throughout an entire generation, and yet longer; nor can we now assert without chance of dispute what cells are mainly concerned in the formation of new tissue. When we examine newly formed granulation-tissue we can distinguish cells of more than one type—(1) small round cells with polylobular and fragmented nuclei, (2) other cells containing oxyphil granules, (3) larger cells with a single nucleus and a relatively large quantity of protoplasm, and again (4) cells of varying but generally large size, varying in shape, but on the whole having the appearance of spindle-cells with single oval nucleus and abundant protoplasm. These can be made out easily.

The first two forms of cells are clearly hæmatogenous leucocytes. Further study of their fate shows that they disappear; they play no further part in the organisation of the tissue save that, as is well shown by Scheltema and Nikiforoff (170), many of them are absorbed by the growing connective-tissue cells, and thus would seem to aid in their nutrition. The last form likewise presents, as such, no difficulties. These are fibroblasts—cells in the process of growth into connective tissue. But what is their relationship to the previous form,—to the round mononucleated cells with fairly abundant protoplasm,—

what are these last, and what, in short, is the origin of the fibroblasts,—is it from leucocytes or from pre-existing connective-tissue cells? Upon this most difficult question more ingenuity and more research have been expended than upon any other part of this well-worked field of inflammation.

There can be no doubt now that a large proportion of the fibroblasts in granulation-tissue are developed from pre-existing connective-tissue cells. The general con-

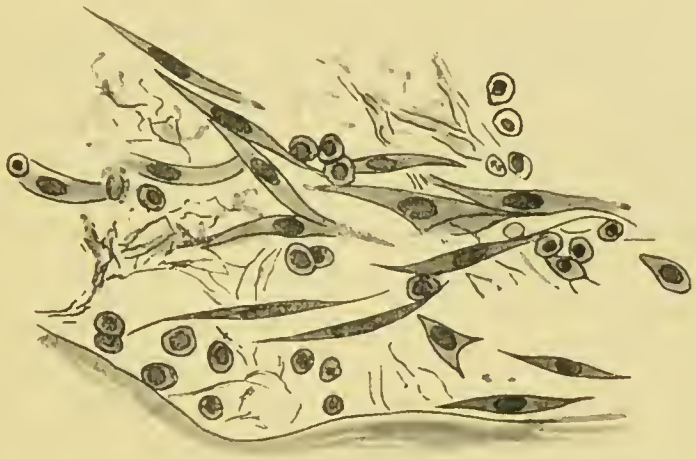

FIG. 18.—Spindle-cells and developing connective tissue in an air-sac of a piece of hardened lung introduced into the peritoneal cavity of a guinea-pig, showing well early stages of development of the fibroblast (seventh day). The cells lie in a network of fibrin.—MARCHAND.

sensus of recent researches leads decidedly in this direction; and it is from the laboratory of Ziegler, who by his classical observations led pathologists for some years to hold the contrary view, that the studies have emanated which most conclusively show the part played by the connective tissue; the researches of Krafft (171), Podwyssozki (172), Coen (173), Fischer (174), and Nikiforoff, confirmed and strengthened by the researches of Arnold (175), Marchand (176), Reinke (177), and Sherrington and Ballance (178), and the more recent researches of von Brunn, Maximow, Mönckeberg, and a host of other

workers, all bring forward evidence in one direction. It is the clearly recognisable pre-existing cells of the tissue —connective, endothelial, and epithelial—which show most constantly the signs of nuclear division: every stage of enlargement, mitosis, and cell-division can be made out in them. Even if we did not possess the information afforded by nuclear changes, the fact that new tissue is always developed in the immediate neighbourhood of pre-existing tissue would in itself point strongly to this same conclusion.

We may rest assured of this much. But can we advance further, and state that all newly formed connective-tissue cells originate from the pre-existing cells of the tissue, and that none of them are derived from wandering cells? In the present state of our knowledge the answer to this question must be an unhesitating "No." We have evidence, in the first place, that cells of the hyaline mononuclear type show all transitions from round- or spindle-shaped cells to definite fibroblasts in the process of forming connective-tissue fibrillæ (Maximow and others). Metchnikoff has followed day by day the transition from the interstitial wandering cell of this type into the connective-tissue cell; this in the tadpole's tail. Evidence was brought forward (*vide* p. 69 *et seq.*) that these hyaline mononuclear cells are histogenous, developed from pre-existing tissue, more particularly from connective-tissue and endothelium. The proliferated and "embryonic" endothelial cells of vessels have been observed in the process of migration into the surrounding area; in short, proliferating tissue-cells in an area of inflammation, in the process of forming new cells, revert to a simpler, more embryonic type; they become round cells of the order of leucocytes: they exhibit phagocytic properties; they give off pseudopodia; they are capable of movement and translation; they

become, for the time, wandering cells. And other cells of the same order, the hæmatogenous mononuclear leucocytes, which, as has been pointed out, are presumably of like endothelial—*i.e.* connective-tissue—origin, when they migrate into an area of inflammation have like properties. There are, in short, histogenous wandering cells, and, once this is admitted, active controversy, save on matters of detail, comes to an end. It may be stated that the fate of these histogenous wandering cells is a matter of environment, of relative position; if they remain in the neighbourhood of the vessels of the inflammatory zone, they are able to develop into fibroblasts, and give origin to new tissue; if, being of endothelial origin, they find themselves lying over a surface they form endothelium; if they wander further afield into the area of inflammatory necrosis they continue to comport themselves as wandering cells, at most acting as phagocytes, and undergoing eventual dissolution, or, more rarely, finding their way back into the vascular system. Thus it is that, as already stated, new tissue is laid down always in the immediate neighbourhood of pre-existing tissue; that is to say, in the neighbourhood of blood-vessels and of adequate nutrition.

This, I believe, expresses the outcome of the more recent studies upon the matter, and to epitomise we may say:—

1. Two series of changes may occur in the cells of an inflamed tissue, which may be included under the terms degeneration and regeneration respectively.

2. The extent to which one or other of these series of changes predominates varies with the nature and intensity of the irritant.

3. Degeneration and death of the tissue-cells may be a direct and immediate result of the presence of the irritant, and then can scarcely be regarded as essential

phenomena of inflammation. Or they may be of more gradual onset, associated with evidence of over-stimulation and increased activity of the cells.

4. Fatty, cloudy, hydropic, and mucoid are the most frequent forms of degeneration affecting the tissue-cells in acute inflammation; hyaline in chronic; other forms are rare.

5. The ultimate fate of the necrosed cells varies as the situation, intensity of irritant, and specific character of the irritant.

6. Cell-proliferation is so constant an accompaniment of certain forms of inflammation that it is impossible to regard this as an adjunct and not as an essential part of the process.

7. The tissues which show the greatest potentiality for reproduction in consequence of inflammation are those which are least highly organised.

8. The origin of fibroblasts and new connective-tissue cells is still in some details a matter of controversy, but this much would seem to be clearly demonstrated: That while the larger proportion of the fibroblasts are derived from the pre-existing connective-tissue cells of the part, others may have originated from histogenous wandering cells that have migrated from some distance. Free haematogenous leucocytes (polymorphonuclear and eosinophil) do not give rise to new tissue; whether lymphocytes can do so is still under debate. Not a few observers have declared that the plasma-cell can elongate, become spindle-shaped, and eventually develop into a connective-tissue cell. Schridde shows that while it is true that these may take on the form of spindle-cells within the tissue, they maintain throughout their specific granulation and are at all periods distinguishable from the connective-tissue cell proper. They come to rest, that is, within the tissue, but do not become converted into

tissue-cells proper. The practical identity between young cells of hyaline mononuclear type and newly proliferated connective-tissue and endothelial cells makes it impossible to determine with precision the point of origin of any individual cell by histological methods alone.

CHAPTER XXIII

ON FIBROUS HYPERPLASIA AND ITS RELATIONSHIP TO INFLAMMATION

The succession of changes from embryonic cells to fully formed tissue can best be studied in cases where there has been a relatively large area of destruction—as, for example, after severe burns, or excision of organs or large portions of organs; or, again, where inflammation has been of a chronic character.

Granulation-tissue can be studied well in the granulating wound, a form of inflammation regarding which, as yet, we have said very little, frequent though it is in surgical experience. When, through injury, the skin or superficial protective layer of a part is removed or destroyed, and the underlying tissue exposed, the first stages are those already described, namely, of dilatation of the vessels in the immediate neighbourhood of the injury, exudation of fluid, migration of leucocytes, and so forth. The extent of the migration depends largely upon whether the wound has become infected or no; but even where infection from without has been prevented, in every case where deeper layers are exposed, and not brought together, there is a certain amount of diapedesis, apparently induced by the presence of products of cell- and tissue-destruction. Where superficial infection takes place, the migration of leucocytes is much more abundant,

and in place of a thin layer of exudate tending to undergo coagulation and form a scab, there is a surface accumulation of pus, without coagulation. With the

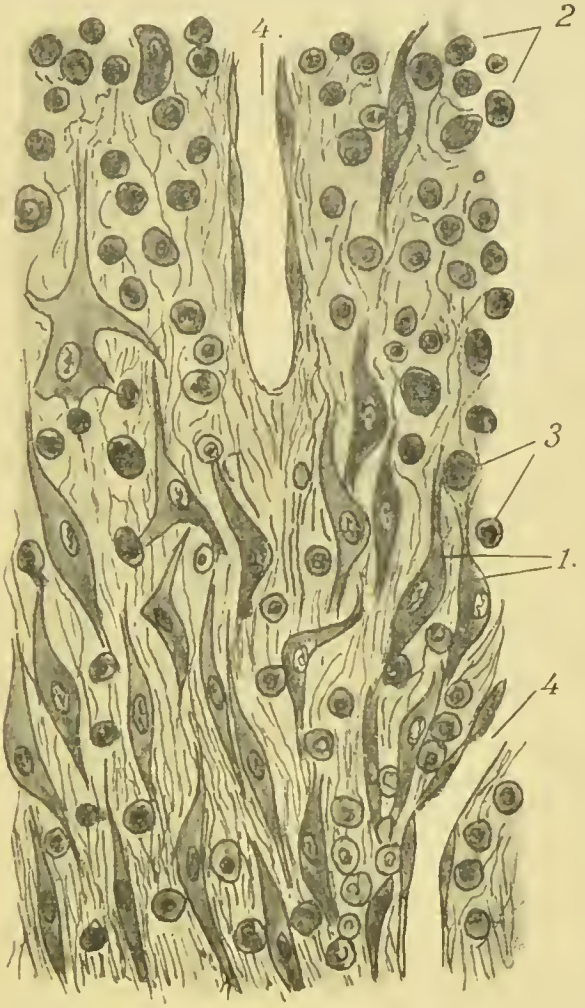

FIG. 19.—Granulation-tissue seen from the deeper toward the upper surface. 1. Spindle-cells, most abundant in deeper portions, where they are also becoming swollen; 2. Polymorphonuclear leucocytes, most abundant towards outer surface; 3. Lymphocytes; 4. Capillaries.—After RIBBERT.

present aseptic methods of treating wounds we are not accustomed to see now any abundant development of pus over an exposed wound. Formerly it was different, and a distinction was made between laudable and foul

pus; the former being bland, creamy, and of sweetish odour; the latter discoloured and foul through the abundance of putrefactive microbes, and accompanied by progressive breaking down of the tissue bordering on the wound. "Laudable pus" seems to us to-day a misnomer. With modern methods pus is regarded as matter out of place and far from praiseworthy. And yet more than one recent observer has shown, by direct experiment, that pus of this nature on an exposed surface has properties which we cannot describe as other than laudable. It has been shown to act as a barrier. Add to such pus covering a granulating wound a suspension of some known pathogenetic microbe, and, unless these be added in excess, they do not set up general infection; they are not to be detected in the underlying tissue. Pus is definitely bactericidal. It would seem that the underlying, newly formed granulation-tissue partakes also in these bactericidal properties (Jürgenlünas (179)).

For beneath this surface layer new tissue begins to form. The process of growth is seen to originate in the immediate neighbourhood of, if not in direct connexion with, the layer of dilated capillaries immediately bordering upon the wound. As already described, these project outwards towards the exposed surface, and from them are developed or projected new capillary loops. As these form there is a rather remarkable clearing in their immediate neighbourhood. The abundant leucocytes and fibrin (if present) or cell-debris disappear, and whether by phagocytosis, autolysis and dissolution, or by re-migration of the still active leucocytes into the vessels, the area immediately around the capillary loop becomes relatively free. From the first series of capillary loops other capillaries are projected, until the whole surface of the tissue, when cleansed, if necessary, of overlying pus, is seen to be covered with a finely granular or coarsely

velvety, reddened, injected layer. This is granulation-tissue.

If healthy granulation-tissue be examined, the proeess of growth is seen to originate in the immediate neighbourhood of, if not in direct connexion with, the dilated new capillaries. It is around these vessels, formed of little more than a single layer of eells, that the fusiform fibroblasts are in greatest abundance. At a later stage, in regions more remote from the advancing margin of the granulations, the fibroblasts have a more general distribution in the intercapillary spaees, and are more elongated; around them may be seen the earliest wavy fibres of white eonnective tissue. These are essentially of eellular origin—as much so as is the substanee of striated musele-fibres. The elongated fibroblasts not only break or extend at their poles into fine proeesses, but also along their sides the protoplasm undergoes modifieation into fine parallel fibrillæ. With the continuanee of this change the cells become smaller and smaller until little is left but the attenuated nuelei, often so flattened and narrow as to be scareely recognisable. With inereasing age the fibrillar substanee contraets; eertainly the newly formed eicatrieial tissue diminishes greatly in volume, and with this diminution the previous great vascularity of the part disappears; the capillaries shrink until the majority beeome completely oceluded. Thus in plaee of the abundant, soft, and sueculent granulation-tissue, rich in cells, blood-vessels, and exuded fluid, there is eventually a firm, shrunken, anæmie mass of fibrous tissue, with a few flattened nuelei, and rich only in elosely pressed bundles of white, semi-transparent fibrils.

Elastic Tissue.—In the new tissue there may be a certain number of the eoarse fibrils of elastic tissue. The development of these has been somewhat extensively studied of late. The conclusion reaehed is that their

development is governed by cells which so far are not to be distinguished from those forming ordinary connective tissue (186).

Fibrosis.—Fibrous hyperplasia may be met with in almost every tissue of the body as a sequence of very diverse morbid conditions. To speak of it in any case as "fibroid degeneration" is a misnomer. The overgrowth of any tissue, however lowly, is not a degeneration. Fibrous tissue may and often does become the seat of degenerative processes, notably the hyaline; but that is another matter. To regard every condition of generalised or localised fibroid change of the organs of the body as a chronic "—itis" is equally erroneous; for, as we shall point out, there are conditions of fibrosis which cannot be regarded as the result of irritation and injury. And even when everything indicates that the fibroid change is of inflammatory origin, the caution must here be given that unless the condition is progressive, it is a source of confusion to term it a chronic "—itis." It is a mistake to term an old-standing case of complete pericardial adhesion "chronic pericarditis" unless there are indications that the condition is still advancing. The inflammation may have been arrested years previously. Such a state should for clearness be spoken of as "pericardial adhesions" or "old adhesive pericarditis." It is interesting to note the opposed tendencies of the two branches of our profession on this subject; the surgeons strive to restrict the idea of inflammation to acute pyogenetic disturbance, the physicians to extend the idea so as to include all cases of chronic progressive "fibrosis." I will not say that the latter is as untenable a position as the former, for it is a matter of peculiar difficulty and delicacy to state what is and what is not an inflammatory fibrosis; after all, there is more danger of being tossed about helplessly in the

Charybdis of including too little, than there is of striking upon the Scylla of including too much in our idea of inflammation.

Here I wish to point out how divergent are the conditions which lead to fibroid hyperplasia, and to show that there is reasonable ground for not classing all forms under the one common heading, even though the resulting appearances may be undistinguishable, and the effects the same.

Inflammatory Fibrosis.—Let us, in the first place, consider the conditions that are certainly of inflammatory origin. The study of the various stages in the development of a tubercle demonstrates that, in man and most mammals, the first result of the lodgment and growth of the tubercle bacillus in the tissues is to stimulate tissue-formation. Only at a later period, with continued action of the products of the bacillus, does tissue-destruction become manifest; and, even here, in a progressive tuberculosis of moderate intensity, we find that while in the central mass the new tissue is breaking down, at the periphery there is definite formation of new fibrous tissue. It cannot be said that here we have an instance of two processes, of inflammation and repair, going on simultaneously, for, studying a series of cases, we find that so-called repair—the tissue-overgrowth—precedes a so-called inflammatory disturbance—the necrosis and caseation; the same influence causes both conditions. This newly formed connective tissue is clearly a productive fibrosis of inflammatory origin.

Now let us consider what seems to be a very different condition. Where there is atrophy or destruction of sundry motor centres in the brain or section of the lower part of the cord, or destructive lesions affecting the cells of the ganglia of the posterior nerve-roots, there results degeneration and death of the axons forming certain

descending or ascending tracts in the cord; and the death of the axons is gradually followed by replacement with fibrous tissue. Here there has been no irritant from without circulating from the lymph-channels to the fibres and causing their destruction; the degeneration and the fibrosis have followed injury at a distance. Is this "replacement-fibrosis" to be regarded as a form of chronic inflammation? No exogenous irritant has been at work; nay, more, the process is so gradual that often none of the ordinary accompaniments of inflammation are to be recognised. Even in the early stages the indications of hyperæmia, migration of leucocytes, formation of new capillaries, are often of the slightest. But, on the other hand, what distinction is to be drawn between the process seen here and the grosser changes which occur in non-infective infarcts? Where, for instance, a branch of the renal artery becomes plugged by a mass of clot, and—as a consequence of the condition of the renal circulation—the area of kidney tissue served by this branch becomes wholly cut off from its blood-supply and dies, we find that the dead tissue becomes replaced by what is clearly cicatricial fibrous tissue. In such infarcts we can recognise the whole succession of inflammatory phenomena. The capillaries immediately surrounding the wedge of dead tissue become greatly dilated; there is abundant migration of leucocytes into the area; the dead tissues, by their action and by autolysis, become broken down and dissolved, and, coincidentally, the surrounding walls give off new capillary loops into the area. We have, in fact, the formation of granulation-tissue with a resultant fibrous tissue-formation and replacement of the dead by cicatricial tissue which, like cicatricial tissue in general, eventually contracts. Here surely we have an inflammatory process set up by the death of the kidney cells, which, dying, liberate diffusible

irritants, initiating a series of changes in connexion with the surrounding vessels. The changes seen in the cord and in the kidney differ in degree only, not in kind.

We must thus recognise at least two types of inflammatory fibrous tissue-development; the one *productive* or *hyperplastic*; the other, as I have termed it, *replacement-fibrosis*. In the latter the amount of new fibrous tissue developed appears to be in proportion to the extent of the destructive process; in the former, continued irritation leads to an overgrowth not related to previous tissue-destruction.

(1) *Productive Fibroses.*—Among these are to be included various localised fibroses, such as the focal areas of new connective-tissue growth set up by the presence of certain micro-organisms, notably those causing the more chronic types of infective granulomas, as, for example, the tuberculous nodules of the tubercle bacilli; syphilitic gummas; the nodules caused by the presence of leprosy bacilli; the extensive tumour-like masses set up in man and cattle by the ray fungus or actinomyces; the new growths around certain pathogenetic blastomycetes or yeasts, more particularly studied by Gilchrist (181) and other American observers. Similar tubercle-like nodules may be formed around certain pathogenetic moulds (aspergilli) (Boyce (182) and others), and we encounter them also around minute larval nematode worms.

Not unlike these are the *capsular* fibroses, those cases of connective-tissue development forming around the irritant, whether infective or no. Here the zone of tissue-formation is a development of so much new material laid down irrespective of previous tissue-destruction; the thick capsules forming around chronic abscesses and phthisical cavities; around impacted bullets, or, as frequently observed in the lungs, around inhaled

particles taken into the tissues by the agency of the leucocytes.

Here also must be included the fibrous overgrowth due to inflammation of *serous* surfaces, including in this the fibroid thickening of those surfaces and the development of organised inflammatory adhesions. The new formation in some of these cases may be most extensive, more particularly in conditions known as chronic hyperplastic serositis, or as Nicholls (183) has termed it, hyaloserositis; the liver, spleen, or pleura may be covered by a thick layer of dense, hyaline, almost porcelain-like connective tissue laid down in successive layers which may be a centimetre or more in thickness.

With these are to be included the general productive fibroses of inflammatory origin affecting the substance of different organs. Such, for example, is the chronic interstitial pneumonia following upon chronic pleurisy, in which bands of fibrous tissue are laid down along the lymphatics passing from the pleural surface. And here also we may include the generalised interstitial fibrosis of so-called chronic parenchymatous diseases, such as we see, for example, in productive parenchymatous nephritis, in which, secondary to the inflammation of the tissue-cells proper of the organ, there is an overgrowth of the fibrous stroma. It is to be noted that some at least of these later cases must be regarded as admixtures of productive and replacement conditions, there being a coincident destruction of the parenchymatous cells.

(2) *Replacement-Fibroses.*—Here we can distinguish certain well-defined types, though all may be termed cicatricial. Wherever we have breach of continuity in a part, there is a tendency for that breach to be filled up by new tissue. In some cases this new tissue is a regeneration of the higher specific cells of the injured organ. In general, however, it may be laid down that

the more highly differentiated a tissue, the less is the capacity of its cells to regenerate, so that, more often, it is the lower, humbler connective tissue that repairs the breach. Under this heading, therefore, we place cicatrices of various orders, and include, as already stated, the replacement of *dead* tissue seen in a simple infarct, where there has been sudden death of the tissues (necrosis), and the replacement-fibrosis seen where tracts degenerate in the spinal cord, and other cases in which fibrosis follows necrobiosis, *i.e.* slower death of the tissue preceded by atrophy and degeneration. Possibly this is the right place also to include the organisation of thrombi; that is to say, of masses of coagulated blood within the vessels. When the blood thus coagulates, its cells largely break down, so that the fibrinous products may be regarded as non-living necrotic tissue. While this, in part, undergoes absorption, if it be not infected, a portion at least becomes organised by granulation-tissue spreading into it from the vessel wall, and so, eventually, is replaced by a fibroid mass.

We may thus classify the forms so far brought forward as follows:—

A. Productive or Hyperplastic Fibrosis:

1. Localised { focal, capsular.
2. Serous and adhesive { local, generalised.
3. Interstitial.

B. Replacement-Fibrosis.

1. Cicatricial.
2. Post-necrotic.
3. Post-atrophic.

C. Mixed Fibrosis: both processes being in evidence.

Transitional and Non-inflammatory Fibroses.—This does not, however, exhaust all the conditions of connective-tissue overgrowth occurring in the organs of the body. We have, in addition, fibroid neoplasia and fibromatosis. It is difficult in every case to separate these off sharply from the productive fibroses of inflammatory origin, for we have a series of what may be termed transitional forms. Typical, encapsulated, fibroid tumours develop without any clear history or indications of previous inflammation. We have here a neoplastic fibrosis or fibromatosis which, for the present at least, we must sharply distinguish from the inflammatory conditions, and that because, as already indicated, we are ignorant of its causation.

There is, however, a curious condition known as keloid, especially liable to occur in certain races, as among negroes, and in certain families or individuals in whom a very slight irritant, which in ordinary individuals would lead to no ill effects, is followed by a progressive growth of fibrous tissue. The pressure of a basket carried on the shoulder, or even of a collar button on the neck, has been known to set up this localised but subcutaneous-spreading fibrous overgrowth; and, indeed, masses several pounds in weight have been so produced. In a case studied by one of my students, Mr. R. Martin (184), a mere scratch by a pin along the arm led to the appearance, in a few days, of a series of small new growths in the line of the scratch. Here, then, irritation originates a new growth that is wholly out of proportion to the intensity or duration of the irritation. This, however, is not a true fibromatosis, inasmuch as, frequently, the new growth undergoes atrophy and disappears. It is an intermediary condition between the two processes of inflammation and neoplasia.

As I have pointed out elsewhere, there is yet another

series of cases in which what we may term stimulation rather than irritation—if we can draw a line between the two—is followed by new connective-tissue growth. These cases I can but indicate here. I would only point out that in the ordinary form of arteriosclerosis, for example, fibroid thickening of the intima does not appear to be directly associated with inflammation of this portion of the artery; everything appears to indicate that it is the media that, undergoing degeneration, first gives way, and that the thickening of the intima and the overgrowth of its connective-tissue cells is wholly a compensatory process. I have suggested that, just as in those who are muscular and accustomed to active exertion, we find that the bone, subject to strain at the origin of the various tendons, shows there a marked over-development and growth into definite ridges, or even into processes, so, where the arterial wall gives way, the distending strain to which the well-nourished intimal cells are subjected favours their proliferation and the development, immediately beneath the endothelial surface, of layer upon layer of new cells, until—the area of dilatation being filled up by the new tissue—the calibre of the artery is restored to the normal, and the extra strain or tension upon the intimal cells is removed (185). The recent observations of Jores (186) upon arteriosclerosis demonstrate that this overgrowth occurs also (he holds, mainly) in the muscular-elastic layer of the intima lying immediately within and against the media. As pointed out recently by my colleague, Dr. C. F. Martin (187), an allied fibrous overgrowth of the intima and media of veins is much more common than is usually imagined. Such *Phlebosclerosis* affects more particularly veins that are poorly supported, and this even in young adults; it is unassociated with any obvious signs of progressive inflammation, and must,

Martin concludes, be placed in this group of "strain-fibroses." The overgrowth of fibrous tissue around the veins—in the liver, for example—in cases of prolonged chronic venous congestion (where this is not excessive),[1] and that remarkable connective-tissue overgrowth of a part in which there is obstruction to the main lymph-channels which constitutes the common type of elephantiasis, are both, we would suggest, of this same order of new connective-tissue growth, due rather to strain and stimulation than irritation, and so more of a physiological than of a pathological and inflammatory type.

In this connexion may be noted certain observations by Thoma (189). In his wonderfully painstaking series of observations upon arterial changes, he has adduced two cases which he describes as examples of "end-arteritis," but in which the inflammation is not apparent, nor indeed any factor other than altered tension of the arterial walls leading to altered conditions of nutrition. He shows that immediately after birth there is developed a thickening of the intima—a connective-tissue proliferation immediately below the endothelium—of that portion of the aorta lying between the ductus Botalli and the passing off of the umbilical arteries. During later fœtal life the umbilical arteries are the largest branches of the aorta; and, when the circulation through them is arrested, the aorta above is too large for the amount of blood requisite for the abdominal viscera and the lower extremities. The arterial current becomes, therefore, relatively slowed, and presumably, judging by the analogy of what occurs in the adult when large branches of the aorta are

[1] I agree with Rolleston (188) thus far, that advanced and severe passive congestion is not accompanied by fibrosis of the central veins of the liver lobules. I have, however, seen this well marked in cases where there has been a long-continued, slight grade of the condition.

ligatured, the aortic blood-pressure is for a time raised. With this slowing and increased pressure there appears a compensatory overgrowth of the intima leading to contraction of the vessel and its lumen. Generally speaking when the area of distribution of an artery is diminished as, for example, when a limb is amputated, the artery shows a similar proliferation of the intima. In both cases the blood remains healthy, and the intima has undergone no injury; the only recognisable change has been a slowing of the blood-stream, and probably increased blood-pressure; and as the intima is nourished, not through the vasa vasorum, but directly from the main arterial fluid, it would appear that with the slowing an increased nutrition is brought into action. This is Thoma's explanation: mine differs somewhat in regarding the overgowth as resulting from increased strain coupled with increased nutrition. I can see no satisfactory reason for calling either of these cases an endarteritis. It is quite possible that other cases of thickening of the intima are due not to irritation, but to increased nutrition with accompanying heightened arterial tension. The difficulty urged by Councilman (190), that high arterial pressure does not invariably lead to overgrowth of the intima, is not, in my opinion, insuperable. It must suffice if here I point out that it is more than probable that certain cases of so-called endarteritis are in no sense of inflammatory origin, or secondary to degenerative changes. In this connexion it was shown by the late Prof. Roy and myself (191) that when the aorta of the dog is suddenly and greatly constricted, and as a consequence the pressure in the proximal portion of the vessel greatly increased, the plasma of the blood is forced into the cusps of the aortic valves, and vesicles of lymph make their appearance on the under surface in that region where fibroid thickening is most frequent in cases

of chronic high arterial pressure. And I am inclined to consider that some at least of the cases of chronic endocarditis, so-called—the cases in which there is a generalised diffuse thickening of the valve-segments with the non-vascular new fibrous tissue laid down in layers parallel to the surface, the most recent immediately beneath the endothelium—belong to this category of non-inflammatory fibroses.

Thus, to express briefly the distinction that we would draw between inflammatory and non-inflammatory fibrous hyperplasia, I would say that where *local injury* leads to increased nutrition of the connective tissue, with increased functional activity of the cells, the ensuing fibrous hyperplasia is to be regarded as of inflammatory origin; where, on the other hand, local injury is not recognisable as the primary cause of the cell-growth, the hyperplasia must be held to be non-inflammatory. In passive congestion, obstructed lymph-flow, and the moderate increase in strain consequent upon arterial change,[1] as in the cases cited above, we can so far see no cause for the fibrous hyperplasia beyond altered conditions of nutrition, coupled with increased functional activity (strain); there has been no primary lesion in the affected regions inducing the reaction. Such cases must be considered as non-inflammatory.

But while we lay down this distinction, we must impress upon the reader that the last word has by no means been said upon this matter, and that further research may cause a radical reconstruction of our opinions. At present our classification is the following:—

[1] Where a great strain is brought rapidly to bear upon the arterial intima, as in the production of aneurysms, we observe no such thickening and overgrowth on its part.

Forms of Fibrous Hyperplasia

A. *Inflammatory.*

1. Productive.
2. Replacement.
3. Mixed.

B. *Neoplastic.*

1. Transitional, of irritative origin (keloid).
2. Neoplastic proper, of unknown origin (true fibroma).

C. *Functional.*

1. Arterial.
2. Venous.
3. Lymphatic.

VI.—TEMPERATURE CHANGES

CHAPTER XXIV

UPON THE INCREASED TEMPERATURE OF INFLAMED AREAS

Very little has of late been added to our knowledge in this division of our subject: what is to be said appears now to be so well established that I need do little more than state the main conclusions. The long controversy that raged before these conclusions were fully accepted, and John Hunter's original views shown to be in the main correct, scarcely comes within the scope of this article.

1. The temperature of superficial regions is raised, it may be several degrees above the normal, by the onset of inflammatory hyperæmia.

2. The temperature of internal organs when inflamed may be raised above the normal, but undergoes no material increase beyond that of other unaffected internal organs tested at the same time.

3. The rise above the normal, which is often present, is an indication of the febrile state accompanying the inflammation, and not of locally increased heat-production. It is deserving of note in this connexion that botanists have demonstrated clearly that local injury in the higher plants is followed by a local rise of temperature which can

only be the manifestation of local increased activities of cells. In animals it is quite possible, nay probable, that, where the irritation is not too severe, the increased metabolic changes in the cells tend towards katabolism and liberation of heat; but if so, this is so slight, and the heat is so rapidly diffused into the circulating blood that thermometric measurements fail to give evidence of its existence. It may thus be left out of consideration for practical purposes.

4. The increased temperature of superficial areas when inflamed is due, not to the production of heat in the part, but to the increased quantity of blood passing through it. When the congestion is so great that stasis ensues, there may be actual decrease in the temperature of the part.

5. The maintenance of high external temperature may exert a favourable effect upon the duration and progress of specific inflammation. Thus Filehne (192) has shown that the course of experimental erysipelas in rabbits is more rapid and more benign when they are kept at a high temperature than at a low. We possess no clear evidence that this is due to the unfavourable effect of the heightened temperature on the growth of the microbes. Pasteur's well-known experiments (193) upon the production of anthrax in fowls (ordinarily insusceptible to this disease) by lowering their temperature can be explained on other grounds. We have abundant evidence that heightened temperature promotes vascular dilatation: the experiment of Filehne may therefore supply a further demonstration of the favourable effects of dilatation of the vessels and hyperæmia in the inflammatory process; indeed the use of hot air and electric light baths for this purpose are now strongly commended from many quarters.

6. Low external temperature, or the application of cold to the surface, contracts the vessels: hence, upon

the lines of what has already been said, it would appear that

(*a*) It is calculated to diminish the amount of exudation.

(*b*) It has no directly good effect upon inflammation due to the presence and growth of pathogenetic micro-organisms, but may have the reverse effect of preventing the fullest reaction on the part of the organism.

(*c*) Where the irritant does not itself grow and multiply, or present cumulative action, there the application of cold may not only be of no harm, but of positive advantage, by lessening the inflammatory reaction and preventing this, where extensive, from being itself a cause of further injury to surrounding tissues.

A further note upon this subject will be found in the chapter upon the Principles of Treatment (p. 216).

PART III

GENERAL CONSIDERATIONS

CHAPTER XXV

ON THE VARIETIES OF INFLAMMATORY MANIFESTATION

THERE is but one proeess of inflammation, but the manifestations of that proeess may be very various. Here I have only to indieate the main varieties. To give a eomplete elassifieation is impossible unless each separate tissue be taken in order, for eaeh tissue presents peculiarities either in liability to inflammation or in the eourse assumed by the proeess. Even to attempt a elassification in broad outline is beset with diffieulties, for the inflammatory manifestation varies, not aeeording to one or two series of eauses, but aeeording to four at least; the permutations are thus so numerous, and the appearances so varied, that to give an adequate seheme of classifieation would require a diagram in four dimensions. These four causes of variation are—

A. Nature of tissue affeeted. B. Position of tissue affeeted. C. Intensity of irritation, or, more eorreetly, ratio between resistant powers of the organism and intensity of the irritant. D. Nature of irritant.

A. Nature of Tissue affected.—As I have already shown in the first portion of this study, there is in the earlier stages of the process a difference in the reaetion of vaseular and non-vaseular tissues, the one series exhibiting marked congestion and vaseular disturbance, the other not. At a later stage, or in more chronie

irritation, as new vessels invade the non-vascular areas, the changes in the two series do no doubt approximate; but in the earlier stages we may distinguish between an ordinary inflammation and "inflammatio sine inflammatione."

The relative denseness and compactness of the tissues also introduce characteristic alterations: a dense tissue, such as bone, does not show the signs of reaction to injury to nearly the same extent as does a loose tissue—such as the omentum, for example—thus, in the former there may be a process almost as atypical as in non-vascular areas. The rigid framework of a tissue like bone prevents great vascular dilatation and exudation, but at the same time may be the seat of great pain due to action of the concentrated irritant upon the nerve-endings. The loose connective tissue of a structure like the omentum, on the other hand, permits great exudation with little or no pain.

The influence of structure is well seen in comparing the course of inflammation affecting cutaneous, mucous, and serous surfaces respectively. Where we have to deal with cutaneous surfaces, or surfaces formed of squamous epithelium, there the increased exudation, and the resistance offered by the layers of flattened cells to the free exit of the exuded fluid, lead towards the formation of vesicles or blisters. In the case of serous surfaces, which form the walls of a moist cavity, the irritant, affecting primarily but one portion of the surface, is very likely to be borne into the cavity with the exudate and to set up an inflammation extending over a very large portion of the surface. Mucous and cutaneous surfaces, which are not thus the boundaries of cavities, exhibit a more marked disposition to the production of localised inflammation and of ulcers; the superficial layers indeed of a well-formed epithelium or mucous membrane, by the

protective powers of their cells, form a defence against irritation from without: thus the superficial exudate from a region of local inflammation cannot easily produce a superficial extension of the process.

Not only the nature of the tissues, but their function also, profoundly affect the character of the inflammatory manifestation. Thus, excretory organs, by the very nature of their function, during the attempt to remove noxious substances from the system, are especially liable to generalised *parenchymatous* inflammations,—the irritation not being local, but affecting at the same time all the cells whose part it is to take up and excrete the irritant bodies.

B. The Position of Tissues.—It is difficult to consider the position and relationship of tissues as they affect the inflammatory manifestations, without continually touching upon their structure. Nevertheless, the two, though very closely connected, do not go hand in hand.

A familiar instance of modification in form brought about by position is to be seen in the result of suppurative inflammation—in the development of *ulcerous* conditions when the process affects free surfaces, of *abscesses* when it attacks deeper tissues. The process in the two cases is virtually the same: there is the same abundant determination of leucocytes, the same degeneration of them into pus. Yet apart from the gross difference in form, there are minor differences between the two. There is, for instance, relatively much more serous exudation from the free surface of an ulcer than there is into and around an abscess. As a general rule, inflamed tissues near a free surface are the seat of more abundant exudation. Of this liability for free surfaces to be the seat of serous inflammation I have already spoken. The skin, with its thick dermal layer, affords a good example: when the full suppurative stage is not reached, inflammation affecting

the outermost layers of the derma is most often of a vesicular or œdematous character; when it affects the deeper layers of the derma the serous infiltration is less evident.

Yet another example of the influence of position in modifying form is seen in enteric fever. In this malady, the lymphoid tissue forming Peyer's patches becomes the seat of excessive cellular infiltration and proliferation, undergoes necrosis, and is cast off, leaving the well-known ulcers. The lymphoid tissue of the neighbouring mesenteric glands likewise undergoes great infiltration and enlargement, but necrosis rarely implicates the whole of a gland: notwithstanding the previous extensive inflammation, the glands commonly recover their normal appearance and size.

Beyond this there are few broad principles to be laid down concerning the relationship between forms of inflammation and position that do not essentially depend upon the structure and functions of the tissues. Much can be said concerning the intimate connexion between position and liability to inflammation; but this and the allied and most important subject of the protective mechanisms of sundry tissues against injury are away from our present point.

C. The Relative Intensity of the Irritant is a more frequent and potent cause of variation. I have already in several places referred to the ratio between the resistant powers of cells and the intensity or virulence of the irritant as it affects the inflammatory process, and have shown how much that was previously vague has been made clear by bacteriological research; while, at the same time, it has brought home the truth that there is a single process of inflammation, the manifestations of which while varying merge insensibly the one into the other.

Broadly speaking, it may be stated, as a result of these studies, that, *cæteris paribus*, increased virulence of any given microbe or diminished power of resistance on the part of the organism or of the tissues, leads to corresponding alterations in the phenomena of inflammation at the region of inoculation; and *vice versa*.

Thus, if a pathogenetic microbe, such as that of anthrax or erysipelas, be greatly attenuated, the effects of inoculation into the subcutaneous tissues may be scarcely recognisable. If the attenuation be not so extreme, some hyperæmia, a determination of leucocytes, and, relatively, very little exudation, will be seen; and in the course of a day or two all traces of inflammation may have disappeared. With slightly more virulent microbes the migration of leucocytes may be followed by their breaking down and consequent abscess-formation; with further increase of intensity of action the migration of leucocytes may be wanting, while the exudation extends and the inflammation rapidly spreads and leads to a bacteriæmia. A like series of changes is observable if the strength of virus be constant and animals more and more susceptible (or less and less refractory) be inoculated.

The variation in tubercular lesions, from isolated dense fibroid masses to loosely formed cell-accumulations and diffuse tubercular inflammation, is evidently explicable on this law. The law holds good also, not merely for bacterial products, but for other irritants. The effect of croton oil varies with the strength of the solution applied; and, as shown by Samuel, according to the condition of the animal. The same is true of abrin and other vegetable extracts.

Turning to physical irritants, while here the intensity of the irritant alone or almost alone is called into play, numerous examples can be given of the effects of variation in this one respect upon the inflammatory manifestation—

effects of cold, for instance, varying from chilblain through inflammatory œdema to gangrene; of heat varying from hyperæmia through vesicular inflammation to complete destruction of tissue; and, again, effects of caustic substances. In this era of aseptic surgery we may forget what was well known to the last generation of surgeons, that caustic substances may be employed either to originate a benign and reparative inflammation (as in the case of indolent ulcers); or, in larger quantities or greater intensity, to bring about a state in which the death of the tissue-elements is far in excess of the subsequent repair. Thus then, according to the above-mentioned ratio, inflammation in a tissue may vary by insensible gradations from a mere hyperæmia up to a spreading suppurative or gangrenous process; and from a purely local manifestation to the development of what may be termed an inflammation of the whole organism.

D. The Nature of the Irritant.—It is clear, then, that it is impossible to base a classification upon the nature of the irritant: the attempt to mark off sharply the inflammations caused by mechanical and chemical noxæ from those produced by bacteria and their products must be given up. Hüter's proposition that suppuration can only be induced by microbes has been repeatedly shown to be erroneous. Thanks more especially to the researches of Conneilman, Leber, Grawitz and de Bary, and Straus (many more names might be mentioned in this connexion), we now know that many chemical substances are capable of causing pus-formation. Among these may be mentioned turpentine, croton oil, mercury, copper, and silver nitrate. While this is so, it must be borne in mind that under ordinary conditions these substances very rarely act upon the organism in a state of sufficient concentration to be pyogenetic. Thus, while it is impossible to make a sharp line of demarcation

between bacterial and chemical irritants, it holds true in the main for man that suppurative disease is an indication of the presence and growth of microbes. On the other hand, although this pyogenetic property is not confined to microbes and their products, yet among microbes it is not the common property of all. Some, like the bacillus of tetanus, never in themselves induce pus-formation: others, like the bacillus of tuberculosis, lead characteristically to tissue-growth and the formation of inflammatory neoplasms rather than to pus-formation. Even among those which, like the micrococci, are highly pyogenetic, the formation of abscesses only occurs when there is a definite relationship between the virulence of the microbe and the resistance of the organism. The reverse is equally true, that numerous microbes, not specially pyogenetic, produce pus under peculiar conditions. Thus, the bacillus typhosus, when it multiplies in the middle ear, induces a suppurative otitis, and is further capable of originating a suppurative arthritis and the formation of abscesses in various tissues.

In fact, under varying conditions the same microbe can induce very various forms of inflammation. Thus, Charrin (194) has shown that the B. pyocyaneus and its products are capable of inducing in one organ—the kidney—pathological conditions so diverse as acute, chronic, parenchymatous, interstitial, and thrombotic nephritis, with, in addition, cyst-formation and amyloid degeneration.[1] This same microbe can induce acute suppuration in the anterior chamber of the eye; and when inoculated into the blood cause a hæmorrhagic inflammation of the serous surfaces. Hence we can proceed farther and state that no strict classification of inflammation can be made according to the nature of the

[1] These changes are comparable with the diverse conditions of the kidney in the human being brought about by the scarlatinal virus.

bacterial irritants; it is, however, possible to make a general grouping of those affecting man, as follows:—

(i.) Micro-organisms characteristically leading to pus- and abscess-formation—Staphylococci and streptococcus pyogenes, B. anthracis.

(ii.) Those leading to abundant exudation with necrosis —B. of malignant œdema.

(iii.) Those leading to cellular infiltration without usually causing abscess formation — B. typhosus, M. gonorrhœæ, B. diphtheriæ, etc.

(iv.) Those inducing characteristically the development of inflammatory neoplasms — B. tuberculosis, B. pseudo-tuberculosis, B. mallei, Actinomyces, Aspergillus fumigatus.

Similarly, chemical substances may roughly be grouped into—

(*a*) Substances causing so slight an irritation when introduced into the organism as to induce cellular overgrowth only in their immediate neighbourhood—such as bland foreign bodies, bullets, etc.; inhaled particles of coal, stone, iron, and the like, conveyed into the pulmonary lymphatics.

(*b*) Substances leading to vesicular inflammation, for example, blistering agents, such as cantharides. (This result, however, depends more upon the position than the nature of the irritant.)

(*c*) Substances leading to cell-necrosis, followed by the formation of granulation-tissue—caustic agents.

(*d*) Substances leading to cell-necrosis and suppuration, such as copper, mercury, mineral acids, etc. (a very rare result in man).

These lists, from the considerations given above, are necessarily unsatisfactory and imperfect.

Other Considerations.—Among other factors modifying the inflammatory process may be mentioned the

duration of the action of the irritant, which of necessity must modify the extent of the manifestations of disturbance in the tissues. A simple aseptic incision, for example, leads to a much milder and slighter series of changes than do the prolonged presence and growth of the tubercle bacillus. And in general it may be stated that mechanical causes of injury set up the simplest forms of inflammation—those unaccompanied by suppuration, unless secondary infection ensues. To state, as laid down by some authorities, that mechanical injuries do not induce inflammation, is wholly opposed to the conception of the process here accepted. Even the simplest fracture of a bone, for instance, is followed by dilatation of the vessels of the surrounding parts, by exudation, diapedesis of leucocytes, and indeed by all the cardinal symptoms whether of the old or the more modern school. While at first it might appear an easy matter to name case after case where the irritant has but a momentary action, upon further consideration it is found that, in the majority of cases of purely mechanical injury, this is not the case; or, to express the matter more exactly, in the case of physical injuries, it is not the act of wounding that causes the inflammation, but the damage inflicted upon the cells of the tissues; as, to a very large extent, inflammation is set up by the products of the injured and destroyed cells. A bone may be suddenly broken, and, nevertheless, even in the most favourable circumstances, pain, swelling, and congestion may affect the region of fracture for several days. One or other region of the body may be rapidly frozen: the inflammation does not manifest itself till after the physical agent has ceased to act, but it continues for hours, and even for days.

There are, moreover, physical irritants of another nature producing definitely chronic inflammation; I refer

to foreign bodies which have gained an entrance into the system. These if bland in themselves may nevertheless cause irritation. A good example of the extensive inflammation which such bodies may set up is seen in the dense fibrous interstitial tubercular masses developed in the lungs of stone-masons around fine silicious particles carried into the lymphatics from the alveoli.

From such examples it will be evident that no satisfactory distinctions between bacterial irritants on the one hand, and physical irritants on the other, can be founded on the duration of irritation. This factor plays no easily recognised part in determining the various forms of inflammation, and consequently I have forborne to place it in the list at the beginning of this chapter.

In thus passing rapidly over the influence of each of the four main causes of variation I have of necessity excluded sundry forms of inflammation due to the combined action of two or more. There are, for instance, such well-marked forms as the *catarrhal* and *croupous*, due to the interaction of all four factors: embolic inflammation and lymphangitis have also been passed over; these, however, are not so much forms of inflammation as inflammatory processes occurring in special regions as a result of special methods of conveyance of the irritants.

The factors then are so many, and their interaction so varied, that anything approaching to an orderly classification is hopeless. What I have here written must be regarded, not as an attempt to formulate such a classification, but as an attempt to indicate briefly how the nature and position of the tissues and the nature and intensity of the irritant bring about modifications in the process of inflammation.

CHAPTER XXVI

ON SYSTEMIC CHANGES CONSEQUENT UPON INFLAMMATION

The results of an acute local inflammatory process are not confined to the immediate locality, but associated alterations in the system at large have long been recognised; yet while recognised these systemic changes have been but little studied: I cannot pass the matter over in silence, but my setting forth of it must necessarily be very brief and imperfect.

I cannot here say more upon the effect of local irritation on the nervous system than that, apart from direct reflex action leading to changes of nervous origin in the region of injury and the reflexes affecting associated regions, the higher centres, and through them the system at large, may become affected by paths that it is not always easy to trace.

The disturbances of the nervous system which accompany local injury can be but vaguely and indefinitely described. As regards the secondary effects, the most suggestive work of the late Prof. Roy and Dr. Cobbett (195), and more recently of Crile (196) upon *Shock*, indicate that there is here a rich field for yet further research. Of the changes in the general circulation, and more especially in the circulating blood, thanks to the observations of von Limbeek (40), Rieder (196), Löwit (198), and Sherrington (199) we possess more

exact knowledge; in acute local inflammation of some extent the circulating blood becomes inspissated: by exudation it loses some of its plasma, while the more solid constituents—the red corpuscles—do not escape. The amount of fluid lost to the circulation is not equalised by increased entrance of lymph into the circulation: in one experiment of Sherrington the blood remained apoplasmic (that is, its specific gravity remained heightened) for more than sixty hours after the infliction of injury. This apoplasmia or diminution in the relative amount of plasma in the blood appears to depend in some measure upon the extent of the vascular area involved in the inflammation; for example, Prof. Sherrington shows that when both feet are involved, by plunging the limbs in water at 52° C., the apoplasmia is more severe than in experiments affecting one foot only. Another well-marked change in the blood concerns the leucocytes. As suspected by Löwit and proved by Sherrington, there is, in some forms of inflammation at least, a primary diminution in the number of leucocytes per unit volume of blood (leucopenia), followed by a marked increase in the number of leucocytes in the blood (leucocytosis). The number of leucocytes was in some instances increased sevenfold. In the leucopenia of inflammation, the diminution is chiefly confined to the finely granular oxyphil cells. These observations of Sherrington are confirmed by the observations of Everard, Demoor, and Massart (200).

Whether the diminution be due to disintegration, or to collection in some area of the circulation, is not yet wholly determined; the observations of Muir and others favour the latter view, and indicate the lungs as regions in which the accumulation occurs. The leucocytosis may become obvious within an hour after the establishment of a local lesion; and it may be prolonged for several days,

even in cases where the injury has been of a mechanical nature. Here, again, according to most observers, it is chiefly the polymorphonuclear or finely granular oxyphil cells which increase in numbers. It is interesting to note that coincidently the coarsely eosinophil cells appear to undergo great diminution; in peritoneal lesions these accumulate in the omental and mesenteric capillaries (77). I can do no more than point out the existence of these blood changes, and further that changes in the number of leucocytes in the blood are not wholly accounted for by the number passing from the blood into the inflamed area. It would seem that local inflammation in some way brings about an over-stimulation of lymphoid tissue, notably that of the bone-marrow, whereby an increased number of leucocytes are poured into the blood; or it may initiate increased proliferation of the leucocytes already in the circulation; but how one or other of these effects is produced is at present unknown. Certainly the direct introduction of the products of bacterial growth into the circulating blood may lead to a more or less pronounced and rapid diminution of the number of leucocytes in the blood, and this diminution, as shown by Löwit, may be preliminary to a subsequent increase.

The further important general disturbance associated with local injury, more especially when of bacterial origin, namely, the occurrence of fever, cannot here be considered. Bacteriological studies lead to the conclusion that traumatic fever, at any rate, is largely due to the diffusion in the blood-stream of soluble bacterial products, and of the products of tissue-destruction derived from the inflammatory focus.

CHAPTER XXVII

ON THE PRINCIPLES OF TREATMENT

The subject of treatment is not in any way part of a treatise on the pathology of a given condition. It has, however, to be acknowledged that if the views here propounded and the conclusions reached be correct, they must have a very direct bearing upon the *principles* of treatment, and a few words must be said regarding those principles. If, in the past, when inflammation was regarded as in itself a harmful process, treatment was nevertheless successful, it is obvious that principles and practice cannot have gone wholly hand in hand, and, conversely, that if treatment was carried on with the idea that the process was in itself dangerous, then time and again procedures were undertaken which were not to the benefit of the patients. As a matter of fact, as already indicated, within the last few years extensive changes are coming into effect and are proving themselves advantageous — such as Bier's method of induced hyperæmia, von Mikulicz's of injections to develop the "resistance period," Wright's method of employing the toxins of specific microbes to stimulate increased resistance to the local growth of these microbes, all of which are based on the assumption that inflammation is the reaction to injury, and demand that the right method is not to lessen or arrest but, on the contrary, to stimulate and augment that reaction.

I have recently, in Keen's *System of Surgery*, discussed, at some little length, the application of these principles to treatment. Here I would briefly recapitulate what appear to me the more important deductions.

"Inflammation is a danger signal, but by no means necessarily a danger. Wherever we observe the outward and visible signs of inflammation we have the indications that something abnormal has occurred in the tissues, something which has brought about a reaction on their part." Thus it is our duty to determine as soon as possible what that something is. If we incise or otherwise operate, our object must be not primarily to reduce the inflammation but to remove the irritant. If we determine that operation is inadvisable, then first we must secure physiological rest for the inflamed part, so that there be no waste of energy on the part of the tissues, that energy being devoted to its fullest to counteracting the irritant.

Of equal importance are procedures calculated to improve the general bodily state and promote the wider reaction on the part of tissues at a distance. Here I may refer to my remarks regarding cryptogenic infection (p. 226), and to the necessity of guarding against not merely the entrance into the injured area of bacteria by way of the blood-stream, but also of toxins and deleterious diffusible substances from the same source. From this it follows that the general health of the patient must be fostered, that the external hygienic condition must be made as good as possible, that the food given be bland, that the bowels be kept open, and the other excreting systems brought, where possible, into free action. Where in addition to local injury the development of fever indicates that toxins are becoming diffused from the inflammatory focus, it is necessary to proceed further and promote, not merely free, but increased excretion through the kidneys, bowels, and skin, by the employment of

copious fluid given by the mouth (or in the form of enemata or subcutaneous injections), of diuretics, sudorifics, etc. What steps shall be taken in addition to these general procedures must be determined by the extent of the reaction observable. All must depend upon whether that reaction is

i. Adequate.
ii. Inadequate.
iii. Excessive.

i. The cases of adequate reaction are those which many surgeons in the past have been inclined to exclude from the category of inflammations, and that because they call for no operative interference. Here are to be included the natural, uneventful healing of wounds, fractures, etc. Save for measures calculated to promote general and personal hygienic and physiological rest, such cases are wisely left to nature.

ii. *Inadequate.* Paradoxical as it may seem, the majority of cases of pronounced inflammation are examples not of excessive but of inadequate reaction. The very extent of the disturbance and its tendency to spread are in themselves indications that the system is for the time unable to counteract the irritant. The irritation may be excessive, but that is another matter. Hence the indications are (1) if possible to remove the irritant; (2) to promote and not reduce the inflammatory manifestations; (3) to aid as far as possible the general reaction on the part of the organism. Here we have the rationale of Bier's treatment (118), which seeks (and in favourable cases with great success) so to promote the hyperæmic exudation and inflammatory reaction in general, that the first mode of combating the disturbance —that of operative removal of the irritant—becomes unnecessary. Wright's method of cure by injection of

toxins comes under the third heading. In this connexion it may be pointed out that poulticing, the employment of hot compresses, etc., are all means which have been employed for generations to "bring an inflammation to a head," *i.e.* to promote an adequate reaction. The employment of simple laparotomy to heal local abdominal tuberculosis is another example of the same principle.

iii. *Reaction in excess* is the exception, not the rule. We do not observe it in the early stages of the process so much as in the later, in the production, for example, of exuberant granulation tissue, in the development of keloid, in the productive overgrowths of chronic inflammations, which, as we have pointed out, appear to pass imperceptibly into the class of new growths, and are to be regarded as indicating an idiosynerasy on the part of the tissues of the individual whereby a minimal irritation has initiated persistent overgrowth. At most we note in acute cases that one factor in the process may be unduly exalted as compared with others, so that the vitality of the tissues is imperilled—excessive hyperæmia may pass on to stasis and necrosis, there may be excessive deposit of fibrin, and so on, and means, where possible, must be taken to regulate the process. Another group of cases would seem undoubtedly to be the series of sympathetic or referred inflammations, in which parts, whether surrounding the injured area, as in the case of the joints, or at a distance, but innervated from the same region of the cord, show the symptoms of an acute inflammation when they themselves have undergone no direct irritation. A knee, or an ankle, for example, which has suffered a relatively slight mechanical injury of the joint-surfaces or ligaments, may rapidly present intense swelling and redness of the surrounding parts. Such in the absence of any treatment tends to bring about immobilisation and physiological rest, but where recognised it may safely,

I think, be dispensed with, provided physiological rest may be gained by other means.

It is in these cases of excessive hyperæmia tending towards stasis (as suggested to me by my colleague, Dr. G. Armstrong) and of referred inflammation that the reduction of the hyperæmia by the application of cold would clearly seem to be the proper practice.

In chronic inflammation it cannot be said that there is any direct treatment. If fibrosis has occurred we cannot directly cause its absorption. We have, it is true, evidence that fibroid tubercles and fibroid adhesions may eventually disappear; we cannot bring about this result with certainty in any particular case. At most we can endeavour to improve the circulation in general, and by that and other means improve the vitality of the tissues and favour the removal of the irritant, as also by the employment of drugs, such as potassium iodide, we can strive to promote absorption. Electricity, active and passive movements, and massage are all useful auxiliaries. Vesicants, rubifacients, setons, and counter-irritation have all been employed towards the same end.

CHAPTER XXVIII

ON ADAPTATION: CONCLUSION

It will be seen that the picture of inflammation here given is very different from the old view in which the dominating idea was that inflammation is essentially an injurious process leading to cell- and tissue-destruction. Here we regard the *irritant* as capable of causing cell- and tissue-destruction, and so long as the irritant is in action so long may this destruction continue. But inflammation itself we regard as the series and sum of the reactive processes set up in the tissues, and then bringing about, not destruction, but the very reverse. Taking as our definition that inflammation is the response or reaction to injury, we are inevitably led to see that this response results in counteracting, or more exactly in tending to counteract, the deleterious effects of the irritant; the inflammatory process tends towards repair. It may not result in repair, for, as we have pointed out in several instances, too often the reaction is either inadequate or excessive. The exudation may possess but slight bactericidal powers, or may be poured out in such quantities that the microbic irritant, instead of being retained in the region of injury, is conveyed outside that region; the wandering cells, instead of destroying, may undergo destruction; they may incorporate bacteria, but not be able to annihilate them;

the fixed cells may either form an incomplete cicatrix, or continue to proliferate in excess. Attempt at repair is not repair. Notwithstanding, studying the various factors involved, it is forced more and more upon us that each tends in one definite direction, and the sum of the process is reparative.

This conception of the process of inflammation has met with considerable opposition. It is urged that, to consider inflammation as an attempt at repair is teleological, *i.e.* is to assume that each reaction in the process is, in itself, purposeful. And, carrying this objection to its ultimate end, "you conceive," say the critics, "that the leucocyte is endowed with intelligence so that it recognises in the microbe a foe to the organism: scents it from afar; hunts, seizes, and digests it, and then, its duty done, its mission in life fulfilled, it withdraws its pseudopodia and dies contentedly."

It is needless to say that we hold no such views regarding the intelligence of the leucocyte. At the same time we unhesitatingly regard inflammation as purposeful —every whit as much as we regard the iris, with its contraction and dilatation under different intensities of light, as subserving a purpose, or the acts of feeding and digesting as being with purpose. Inflammation is a physiological process in so far as it is the calling into action, in response to accustomed stimuli, of properties normally possessed by the tissue; it is a pathological process in so far that, while the stimuli are in kind not different from normal stimuli, in intensity they are greater. If we admit physiological purpose, we must admit pathological. This may, indeed, be laid down regarding all pathological conditions, namely, that in them we are not dealing with the effects of new and unaccustomed factors, but with the ordinary factors telling upon the tissues in an abnormal way, being either

deficient or excessive in their action. Within physiological limits, the reaction to a given stimulus is nicely balanced and adequate; when the stimulus is excessive, the reaction is liable to be imperfect. The iris accommodates and adequately protects the retina within certain limits, but, if the eye be exposed to too intense a light, the iris fails to arrest all the rays and the retina suffers. And so it is that, in inflammation, when the stimuli are excessive and so have become irritants, the tendency is for the reaction not to be perfectly balanced, and the ultimate result to be an incomplete counteraction of the disturbance. But, to repeat, if we recognise purpose in the one set of cases, we must recognise it in the other.

All, it will be seen, depends upon what is our conception of "purpose" in vital phenomena. That conception is teleological if and when we regard it as primary —as what may be termed an intelligent endeavour on the part of the tissue to accomplish a certain object—a predetermined end. To suppose that, in inflammation, the vessels dilate and bring about increased exudation *in order to* flush out the irritant, is an utterly wrong and baseless idea. If, on the other hand, our conception is along these lines—that in the course of evolution those individuals survived who, by chance, let us say, happened to manifest this reaction on the part of their vessels in response to stimuli of a certain order, whereas those who did not were more unfavourably placed and so succumbed; that they conveyed the same power to their descendants who also possessed this advantage over individuals incapable of affording the reaction; then we can conceive the development of a race possessing a mechanism for countering a given stimulus by a given reaction, a race in which provision is made, or gained, for dealing with a given order of events; then it will be seen that what primarily is accidental becomes secondarily purposeful

through the survival of the fittest and the inheritance of defensive acquirements. The tissues thus become prepared to respond to certain alterations in their environment. In other words, "natural selection" renders what was primarily accidental, secondarily purposeful.

The whole process of inflammation is an exemplification of "adaptation," and we would strongly commend the address by Prof. Welch (201) upon this subject to those desirous of gaining a right point of view regarding pathologieal processes in general. For living matter to survive, it must be adapted to its environment, and this, in the first place, happens through inheritance, through the survival of the fittest, along the lines laid down above.

Yet, in the study of inflammation, we are compelled to recognise, not merely inherited, but also individual adaptation. We cannot otherwise explain why it is that bacteria, which at first exhibit active local growth within the tissues, become eventually destroyed on the resolution of the inflammatory state, unless we acknowledge that the cells, or certain of them, acquire and, it must be, transmit, increased bacteriolytie and antitoxic properties. The facts gained regarding the development of immunity—the presence in the body-fluids of the immunised animal of substances inimical to the infective agents, which are absent, or present in but minimal amounts, in the fluids of the untreated animal—all demonstrate this individual adaptation. At the present time, indeed, workers all over the civilised world are busy in researches bearing upon this very subject, the production and mode of action of what may be termed, generically, anti-bodies.

Here I can do little more than mention certain general laws which seem to be at work in bringing about, or favouring, individual adaptation.

1. The first is that of *reserve force*. No cell—and no tissue—normally is in action to the limit of its

powers; on the contrary, normal activity is far below what the cell is capable of performing. In other words, normal stimuli do not induce a maximal reaction, and, therefore, irritants—excessive stimuli—up to a certain limit, do not overwork, and do not lead to disintegration of the cell. Perhaps the greatest difficulty encountered by most students of medicine in accepting the facts of phagocytosis lies in this, that, regarding the tissues as normally sterile, they cannot comprehend the assumption of what appear to be totally new properties by the leucocytes and other cells in inflammation and infection, namely, the assumption, as they regard it, of phagocytic powers and the taking up of pathogenetic bacteria. But, as a matter of fact, this is no new property. Throughout life the cells are engaged in digesting bacteria. We find phagocytic leucocytes passing out and free upon mucous surfaces—any smear or swab from the pharynx will show these leucocytes with their contained bacteria. As Ruffer (202), Nicholls (203), and others have shown, bacteria are to be seen in the lymph-glands and along the lymphatic channels of healthy animals, and these, most often, within cells. As Ford (204), working in my laboratory, has demonstrated, using the fullest precautions against contamination, bacteria can be cultivated from the liver and kidneys of more than 50 per cent of the apparently healthy animals of the laboratory; and that the bacteria so obtained are not contaminations is proved by the remarkable regularity with which each different species presents a different bacterial flora. Having followed Ford's observations and seen the care with which they were conducted, I cannot accept the observations of those who refute his work. As Wrosczek (205) has recently shown, if animals be fed with non-pathogenetic germs, or germs setting up no recognisable intestinal disturbances, colonies of the species so injected are, later, to be gained from the

various organs of the apparently healthy animals. The tissues are *potentially* sterile; that is, the leucocytes and other phagocytic cells are, throughout life, engaged in destroying bacteria which have gained occasional entrance into the tissues (206). When a few intensely virulent bacteria gain this entrance, or a large number of a less virulent form manage to grow in some one or other locality, and thus set up inflammatory changes, the above-mentioned reserve force in the phagocytic cells comes into play and permits these cells to take up and digest the greater numbers or the more toxic forms. It is this circulation of potentially pathogenetic microbes that explains the *cryptogenic* infections of internal organs.

2. The second law is that of *accustomance*. A cell not actually destroyed by any deleterious agency is apt to become accustomed to the presence and action of that agency. What is the basis of this accustomance it is difficult to say, though it is not difficult to suggest a hypothesis or hypotheses. Here I simply state that this is an observed law, a law best exemplified in what has been made out regarding the conversion of a negative into a positive chemiotaxis.

3. The third and very important law, somewhat closely allied to the last, is that of *habit*, or, as Fraser Harris (207) has termed it, "vital inertia." According to this law, when once, through a given stimulus, a certain series of molecular changes is set up in a cell, those changes are liable to continue after the stimulus has ceased, and, if the stimulus be sufficiently strong or sufficiently often repeated, the cell acquires the habit, or property, of setting in action a particular series of molecular changes after a minimal stimulation. This is, perhaps, best exemplified in connexion with our subject in the production of antitoxins. It is found that, once the diphtheric toxin, for instance, has stimulated the cells

of the organism to produce antitoxins, that production continues and is wholly out of proportion to the amount of toxin introduced; while, similarly, once an animal has gained full immunity against any organism, it only needs the introduction of that micro-organism into the system to induce an immediate reaction, whereas previously days or weeks had been required for accustomance and counteraction to be adequately developed. The existence of this law was first recognised by Weigert (167); it may be said to form the basis of Ehrlich's side-chain theory of immunity.

Hence, to sum up, while I would not give this as a definition (as I did in a previous edition), for I see the force of Ainley Walker's argument that, in a definition, one should state what a thing is and not what it tends to bring about,—my conception of inflammation, from all the considerations here laid down, must be that it is *the series of changes constituting the local manifestation of the attempt at repair of actual or referred injury to a part*, or, briefly, as *the local attempt at repair of actual or referred injury*.

And in conclusion let me lay stress upon what I regard as the main outcome of this essay. In studying the reactions of the organism to injury, we must be impressed by the multifariousness of natural processes; the end may be attained, not in one way only, but in many. It is not by cells of one order alone—by phagocytes—or by leucocytes in general and only leucocytes, or merely by the reaction on the part of the fixed cells of the tissue, or by vascular changes alone, or by altered temperature, or solely by the chemical and mechanical action of the exudate that repair is effected. All means are employed to antagonise the irritant and to effect healing. The cells of the body, fixed and free, play their part; the nervous system aids the process; the bodily humours

render efficient help; modifications in the vessel-walls and blood-stream are valuable auxiliaries. Diverse processes are employed, now one more particularly, now another, according to the needs of the moment, but none exclusively.

So diverse are the opinions of pathologists upon many branches of this subject of inflammation, and so great is the amount of recent research, that I can neither hope that all the conclusions here set down will gain acceptance, nor that in these pages, inevitably condensed as they are, I have succeeded in recognising and duly acknowledging all work of primary importance. In the rapid progress of our science, much, it may be, that is here set forth will be modified. Nevertheless I hold that the conception of the inflammatory process indicated in this article is that which embraces the largest number of like phenomena, and excludes most satisfactorily those which if associated are unessential: and that it is by the study of cellular pathology in its strictest sense that the surest advance has been and is to be made in our knowledge of this the dominating process in disease.

REFERENCES

1. Sir J. Burdon-Sanderson. Art. "Inflammation." Holmes' *System of Surgery*, 5th edit. London, 1888.—2. Hüter, C. *Allgem. Chirurgie*, Leipzig, 1878: *Grundriss der Chirurgie*, Leipzig, 1880. —3. Zahn. *Inaug. Diss.* Berne, 1871.—4. Grawitz. Quoted by Lubarsch (67).—5. Metchnikoff. *La Pathologie comparée de l'Inflammation*, Paris, Masson, 1892. English transl. by Starling, 1893.—6. Adami. "The Dominance of the Nucleus," *Brit. Med. Journ.* 1906, ii. 1760.—7. Greenwood (Miss). *Journ. of Physiol.* 1886, vii. 254; 1887, viii. 263; 1890, xi. 576; 1894, xvi. 441.—8. Le Dantec. *Ann. de l'Inst. Pasteur*, 1890, iv. 273; 1891, v. 163.—9. Krukenberg. *Untersuch. a. d. physiol. Inst. Heidelberg*, 1878, ii. 273.—10. Reinke. *Untersuch. a. d. botan. Inst. Göttingen*, 1881. —11. Frosch. *Ctbl. f. Bakt.* 1st Abth. 1897, xxi. 926.—Mouton. *Ctes. rend. Soc. Biol.* 1901, liii. 801; see also Gottstein. *Hygien. Rundsch.* 1903, xiii. 593, and Musgrave and Clegg (14).—12. Stahl. *Botan. Ztg.* 1884, Nos. 10 and 12; *Flora*, 1892, lxxvi. 247.—13. Pfeffer. *Untersuch. a. d. botan. Inst. Tübingen*, 1888, ii. 582; *Humboldt*, 1888, vii. 6. See also Engelmann. *Pfluger's Archiv*, 1881, xxv. 285; *ibid.* 1882, xxvi. 537.—14. Musgrave and Clegg. *Rpts. Bureau of Govt. Laboratories*, Manila, 1904, No. 18.—15. MacBride. *Proc. Cambridge Phil. Soc.* 1896, ix. 153.—16. Loeb. *Biol. Lectures, Marine Biol. Lab. Wood's Hole*, 1883. Boston, Ginn and Co. 1894.—17. Messing. *Ctbl. f. allg. Path.* 1903, xiv. 915.—18. Hardy. *Journ. of Physiol.* 1892, xiii. 165.—19. Metchnikoff. *Virchow's Archiv*, 1884, xcvi. 177.—20. Senftleben. *Virchow's Archiv*, 1878, lxxii. 542.— 21. Goecke. *Ziegler's Beiträge*, 1896, xx. 293.—22. Jacobs. *Beitr. z. Histol. d. acut. Entzünd. d. Cornea*,. Inaug. Diss. Bonn, 1887.—23. Cohnheim. *Vorlesungen*. 2nd edit. Leipzig, 1882, transl. M'Kee, New Sydenham Soc. 1890.—24. Councilman. *Boston Journ. Med. Sci.* 1898-99, iii. 99; *Am. Journ. Med. Sci.* 1897, cxiv. 23.—25. Coats. *Pathology*, 3rd edit. 1889, 119.

—26. Councilman. *Virchow's Archiv*, 1883, xcii. 217.—27. Grawitz and de Bary. *Virchow's Archiv*, 1887, cviii. 67; Steinhaus. *Die Aetiologie der acuten Eiterungen*, Leipzig, 1889 (gives full literature to date).—28. Leber. *Die Entstehung der Entzündung*, Leipzig, Engelmann, 1891.—29. Hohnfeldt. *Ziegler's Beiträge*, 1888, iii. 343.—30. Ribbert. *Die Bedeutung der Entzündung*, Bonn, 1905.—31. Wharton Jones. *Phil. Trans. Roy. Soc.* 1846, 64.—32. Schultze, M. *Arch. f. mikr. Anat.* 1863, ii.—33. Ehrlich, P. *Farbenanalytische Unters. z. Histol. u. Klinik des Blutes. Gesamm. Mittht.* Berlin, Hirschwald, 1891; *Charité Annalen*, 1888, xiii. 300; see also Ehrlich and Lazarus. "Die Anæmie," *Nothnagel's Spec. Pathol. u. Therapie*, 1898, transl. as *The Histology of the Blood* by Myers. Cambridge, 1900.—34. Rieder. *Beiträge z. Kenntniss d. Leukocyten*, 1892.—35. Sherrington. *Proc. Roy. Soc.* 1893, 161.—36. Kanthack and Hardy. *Journ. of Physiol.* 1894, xvii. 81, and *Phil. Trans. R. S.* 1894, clxxxv. 279.—37. Hardy. *Journ. of Physiol.* 1898, xxiii. 359; see also Hardy and Lim Boon Keng, *ibid.* 1893, xv. 361.—38. Durham. *Journ. of Path.* 1897, iv. 370; see also Muir, *Journ. of Path. and Bact.* 1901, vii. 161; *ibid.* 1900, vi. 394.—39. Beattie. *Journ. of Path.* 1902, viii. 129.—40. Taylor, A. E. *Contributions from the William Pepper Lab. of Clin. Med.* Philadelphia, 1900, i. 148 (gives full Bibliography to date). For full studies upon the hæmal leucocytes see also Ewing, *Clin. Path. of the Blood*, 2nd edit., Lea Bros. and Co., New York and Philadelphia, 1903; von Limbeck, *Grundriss einer klin. Pathologie des Blutes*, Jena (successive editions), gives a very thorough study of this subject.—41. Schridde. *Anat. Heft.* 1905, xxviii. 2, *Münchener med. Wochenschr.* 1905, Nos. 26, 29, and 39, and *ibid.* 1906, No. 4. Also *Verhandl. der D. Pathol. Gesellsch.* Meran, 1905.—42. Unna. *Monatshefte f. prakt. Dermat.* 1891, xii. 296; *ibid.* xx. No. 7; *Berlin. klin. Woch.* 1892, xxix. 1242; *ibid.* 1893, xxx. 222; *ibid.* 1893, 222.—43. von Marschalko. *Archiv f. Dermat.* 1895, xxx. 3 and 241; *Ctbl. f. allg. Path.* 1899, x.—44. Justi. *Virchow's Archiv*, 1897, cl. 197; for fuller bibliography see Beattie (39).—45. Wlassow and Sepp. *Virchow's Archiv*, 1904, clxxvi. 368; A. Wolff. *Arch. d. Méd. exp. et d'Anat. pathol.* 1903, xv. 713; *Berlin. klin. Wochenschr.* 1901, 1290.—46. Almkvist. *Virchow's Archiv*, 1902, clxix. 17.—47. Paltauf. *Second Inter. Congr. f. Dermat.* Wien. 1892; *Lubarsch-Ostertag Ergebnisse*, Abth. 2, 1895, 261.—48. Maximow. *Ziegler's Beitr.* 5th supplemental Heft, 1902; *ibid.* 1904, xxxv. 93.—49. Cornil and Ranvier. The numerous contributions of these two observers

and their pupils are well summarised in their *Manuel d'Histologie pathologique*, of which a third edition has recently been published, Paris, Alcan, 1902.—50. Ruffer. *B.M.J.* 1902, ii. 491; *Quarterly Journ. of Micr. Sci.* 1890, xxx.—51. Mallory. *Journ. of Exper. Med.* 1898, iii. 611.—52. Adami, Abbott, and Nicholson. *Journ. Exper. Med.* 1899, iv. 349.—53. Werigo. *Ann. de l'I. Pasteur*, 1894, viii. 1; see also Lemaire, *Archive d. Méd. exp.* 1899, xi. 556.—54. Behring and Much. *Prager med. Wochenschr.* 1904, No. 1.—55. Gulland. *Lab. Reps. R.C.P. Edin.* 1891, iii. 106; *Journ. of Path.* 1894, ii. 447; *Journ. of Physiol.* 1895-96, xix. 385; Saxer. *Ctbl. f. allg. Path.* 1896, vii. 421; Uskow. "The Blood considered as a Tissue" (Russian), 1890: various papers by his pupils in the *Arch. d. Sc. Biol.* St. Petersburg, 1893 to 1897; for abstract see Taylor (40). — 56. Muscatello. *Virchow's Archiv*, 1895, cxlii. 327; Graser. *Arch. f. klin. Chirurgie*, 1895, l. 887; *D. Ztschr. f. Chirurg.* 1888, xxvii. 533; Borst. *Virchow's Archiv*, 1900, clxii. 94; see also Marchand. *Ziegler's Beiträg.* 1889, iv. 1; *Sitzungsber. der Gesellsch. gesammt. Wiss. Marburg.* 1897, No. 3; *Der Prozess der Wundheilung*, Stuttgart, 1901; and Roloff, *Habilitationsschr.* 1894, quoted by Lubarsch (67).—57. von Brunn. *Ziegler's Beitr.* 1901, xxx. 417; Moenkeberg. *Ziegler's Beitr.* 1903, xxxiv. 484 (Büttner, *ibidem*, 1899, xxv. 453, gives full literature on this subject to date: this article continues it to 1903).—58. Baumgarten. *Arbeiten a. d. path. Inst. Tübingen*, 1904, iv. 310; *Ctbl. f. allg. Pathol.* 1904, xv. Erganzungsheft, 115. — 59. Pratt. *Johns Hopkins Hosp. Reps.* 1900, ix. 265.—60. Metchnikoff. *Biol. Ctbl.* 1883, 561; *A. de l'I. P.* 1892, vi. 1; *Q.J.M.S.* (new ser.) xxiv. 112; Barfurth. *Arch. f. mikr. Anat.* 1887, xxix. 35; Griffiths. *Journ. of Pathol.* 1894, iii. 131. — 61. Ranvier. *C. R. Acad. des Sciences*, 1889, cx. 165. — 62. Marchand. *Verhandl. d. D. pathol. Gesellsch.* 1902, iv. 124; see also *Der Prozess der Wundheilung* (56).—63. Saxer. *Anatom. Hefte*, 1896, No. 19.—64. Lubarsch. *D. med. Woch.* 1898, 501, 523, 539, 553. A valuable discussion of modern problems in regard to the inflammatory process.—65. Grawitz. *Virchow's Archiv*, 1896, cxliv. 1; *D. med. Wochenschr.* 1896, No. 26; *Ueber Leben und Tod.* Rectoratsrede, Greifswald, 1896.—66. For a study of this form of cell see, more particularly, Arneth. *Die neutrophile weissen Blutkörperchen bei Infektionskrankheiten*, Jena, Fischer, 1904, and *D. med. Wochenschr.* 1904, 92. — 67. Hardy and Wesbrook. *Journ. of Physiol.* 1895, xviii. 490. — 68. Opie. *Trans. Assoc. Am. Physicians*, 1904, xix. 136; *Johns Hopkins Hosp. Bull.* 1904,

15, 71.—69. Maximow. *Ctbl. f. Path.* 1903, xiv. 87.—70. Other articles bearing upon mast-cells are :—Schreiber, *ibid.* 1903, xiv. 913; and Loeb, L., *Journ. med. Research*, 1902, viii. 44.—71. Other recent articles upon the plasma-cell deserving of note are Ehrlich. *Virchow's Archiv*, 1904, clxxv. 198; Herbert. *Monatschr. f. prakt. Dermat.* 1900, xxx. 313, and *Journ. of Path.* 1900, vii. 90. See also Taylor (40); Whitfield, *Brit. Journ. of Dermatology*, January and February 1904, gives a good statement of the different opinions and observations regarding these cells.—72. Borrel. *A. de l'I. P.* 1893, vii. 593.—73. Duenschmann. *Journ. of Path.* 1894, iii. 118.—74. Knud Faber. *Journ. of Path.* 1893, i. 349.—75. The literature regarding giant-cells is given by Marchand. *Virchow's Archiv*, 1883, xciii. 518, up to 1883; and by Hektoen. *Journ. of Exper. Med.* 1898, iii. 21, up to 1898.—76. Gabritchewsky. *A. de l'I. P.* 1890, iv. 346.—77. Roux. *Trans. Internat. Congr. of Hygiene*, London, 1891, ii. 120.—78. Pekelharing. *La Semaine méd.* 1889, 184.—79. Massart and Bordet. *J. d. l. Soc. Roy. d. Sc. Med. et Nat. d. Bruxelles*, 1890, and *A. de l'I. P.* 1891, v. 417.—80. Buchner, H. *Berliner klin. Wochenschr.* 1890, No. 47.—81. Kanthack. *Medical Chron.* Manchester, N.S. 1894, i. 246 and 332.—82. Wolff, A. *Berl. klin. Wochensehr.* 1904, xli. 1105.—83. Macfadyen and Rowland. *Ctbl. f. Bakt.* 1900, xxx. 753; *Lancet*, 1900, i. 849 and 1130; *Proc. R. S.* April 5, 1900.—84. Metchnikoff. *L'Immunité dans les maladies infectieuses*, Paris, Masson, 1902. This work, besides recapitulating the main data given in the former (5), gives in detail M. Metchnikoff's views upon immunity in general, with criticism of opposing theories and bibliographical references.—85. Leishman. *Brit. Med. Journ.* 1902, i. 73.—86. Issaeff. *Ztschr. f. Hygiene*, 1894, xvi. 287.—87. Nuttall. *Ibid.* 1888, iv. 353.—88. Traube and Gschleiden. *Jahresber. d. Schlesisch. Gesellsch.* 1874, lii. 179.—89. von Fodor. *D. med. Wochenschr.* 1887, 745.—90. Nissen. *Ztschr. f. Hygiene*, 1889, vi. 487.—91. Behring and Nissen. *Ztschr. f. Hygiene*, 1890, viii. 424; Behring, *D. med. Wochensehr.* 1891, 655.—92. Hankin. *Proc. R. S. Lond.* 1890, xlviii. 93; *Ctbl. f. Bakt.* 1892, ix. 722 and succeeding volumes; "Discussion on Immunity," *Trans. Internat. Congress of Hygiene, London*, 1891. (This important discussion gives the views of the opposing schools, cellular and humoral—of Roux, Metchnikoff, Behring, Buchner, Hankin, etc. A comparison of the contributions to this discussion with those to the discussions on the same subject at the succeeding Congress at Buda-Pesth (1894), and at the Internat. Med. Congress, Paris

(1900), is of great interest as showing the gradual change in opinions on these topics. Another discussion well worth reading is that held by the Pathological Society of London in 1892 (*B.M.J.* 1892, i. 373, 492, 591, 604) and *Trans. Path. Soc.* 1892). —93. Buchner. *Arch. f. Hyg.* 1890, x. parts i. and ii.; *Ctbl. f. Bakt.* 1889, v. 817; *ibid.* 1890, vi. 1; *Fortschr. d. Med.* 1892, x. 319 and 363; *Ctbl. f. Bakt.* 1894, xvi. 738, etc.; art. "Immunity," *Encyclop. Medica*, Edinburgh, 1900, v.—94. Vaughan, Victor C., and M'Clintock. *Med. News* (N.Y.), 1893, 701. See also Kossel, H., *Ztsch. f. Hyg.* 1894, xvi. and *Arch. f. Anat. u. Physiol.* Physiol. Abth. 1894, 200.—95. Tizzoni and Cattani. *Berl. klin. Wochenschr.* 1894, 64, 189, and 732.—96. Ehrlich. *Gesammelte Abhandlungen*, Berlin.—97. The leading papers on bacteriolysis will be found in (84).—98. Ribbert. *Der Untergang pathogen. Schimmelpilze im Körper*, Bonn, 1887.—99. Denys and Havet. *La Cellule*, 1894, x. 1.—100. Buchner. *Münchener med. Wochenschr.* 1894, xli. 469 and 497.—101. Bail. *Berl. klin. Wochenschr.* 1897, xxxiv. 887.—102. Schattenfroh. *Arch. f. Hyg.* 1896, xxvii. 234; 1897, xxxi. 1; 1899, xxxv. 135. —103. Van der Velde. Ref. in *La Cellule*, 1894, x. 1.—104. Jacob. *Ztsch. f. klin. Med.* 1897, xxxii. 466. See also Hahn. *Münch. med. Wochenschr.* 1897, xliv. 134; Lachtchenko, *Arch. f. Hygiene*, 1900, xxxvii. 290; Trommsdorf, *ibid.* 1901, xl. 382. —105. Löwit. *Vorlesungen ueb. allgem. Pathologie*, Jena, 1897. —106. Bordet. *Ann. de l'I. Pasteur*, 1899, xiii. 15; 1901, 232; *ibid.* 303.—107. Lubarsch. *Ctbl. f. Bakt.* 1889, vi. 841. —108. Gengou. *Ann. de l'I. P.* 1901, xv. 68.—109. A criticism of the facts bearing upon these experiments is given in Jacoby, M., *Immunität und Disposition*, Wiesbaden, 1906, an excellent study of the immunity problem.—110. Pfeiffer. *Ztsch. f. Hygiene*, 1894, xvi. 268; *ibid.* 1896, xviii. 1.—111. Bordet. *Ann. de l'I. P.* 1895, ix. 462.—112. Wright and Douglas, *Proc. R. S.* 1903, lxxii.; 1904, lxxiii. 128; 1904, lxxiv. 147; see also Bulloch and Atkin, *ibid.* 1905, clxxiv. 379.—113. Bulloch. An admirable account of these researches upon Opsonins and Opsonic Treatment is given by Bulloch, *Practitioner*, 1905, lxxv. 589, together with full literature to date. A brief but clear account is also given by Ross, G. W., *B.M.J.*, 1906, 2.—114. Woodhead. *Bacteria and their Products*, London, Scott, 1891. —115. Pawlow. *The Work of the Digestive Glands*, transl. by W. H. Thompson, London, Griffin, 1902, 160; Bayliss and Starling. *Journ. of Physiol.* 1904, xxx. 61. 116. Metchnikoff and Delezenne. *C. R. Soc. de Biol.* 1902, 282.—117. Samuel.

Lubarsch-Ostertag Ergebnisse, Abt. 1895, ii. 65.—118. Bier, A. *Die Hyperämie als Heilmittel*, 2nd edition, Bonn, 1905. (The second edition is much fuller than the first.)—119. Ainley Walker. *Inflammation, Infection, and Fever*, London, Lewis, 1904.—120. Klotz, O., *Journ. Exp. Med.* 1905, vii. No. 6.—121. Halliburton. *Chemical Physiology and Pathology*, Lond. 1891. 340.—122. Reuss. *D. Arch. f. klin. Med.* 1881, xxviii. 317; Hoffmann. *Lehrb. d. Zoochemie*, Vienna, 1879; *Virchow's Arch.* 1879, lxxviii. 250; Mehu. *Traité de chimie médicale*, 1878, 198; Letulle. *L'Inflammation*, Paris, Masson, 1893, 256.—123. Miller, J. L. "Transudates and Exudates," *Amer. Med.* 1904, viii. 835.—124. Welch. The *locus classicus* for a description of the process of Thrombosis in our language is Welch, W. H., article "Thrombosis and Embolism" in Allbutt's *System of Medicine*, vol. vi. —125. Neumann. *Arch. f. mikr. Anat.* 1880, xviii. 130; *Ziegler's Beitr.* 1889, v. 345; *Virchow's Archiv*, 1896, cxliv. 201; *ibid.* 1896, cxlvi. 193.—126. Marchand. *Virchow's Archiv*, 1896, cxlv. 314; Orth. *Göttinger Nachrichten*, 1896, Heft 3; *Ctbl. f. Path.* 1896, vii. 850; Ziegler. *Ctbl. f. Path.* 1896, vii. 849.—127. Gaylord. *Journ. of Exp. Med.* 1898, iii. 1. Gives literature to date.—128. Loeb, L. *Biological Bull. Wood's Hole*, 1903, iv. 301; see also Löwit. *Ziegler's Beitr.* 1889, v. 469.—129. Adami. *Montreal Med. Journ.* 1903, xxxii. 401.—130. Adami. *Philadelphia Med. Journ.* 1898, 373.—131. Salkowski. *Virchow's Archiv*, 1897, cxlvii. 1.—132. Jacoby. *Ctbl. f. allg. Pathol.* 1902, xiii. 2.—133. Conradi. *Beitr. z. chem. Phys. u. Path.* 1901, i. 193.—134. Müller. *20ster Congr. f. inn. Med.* Wiesbaden, 1902.—135. Arnold. *Virchow's Archiv*, liv.; 1872, 1 (*Development of Capillaries*); 1873, lviii. 231 (on *Diapedesis*); 1876, lxvi. 77 (on *Cement Substance*); 1876, lxviii. 465 (on *Lymph-Spaces*).—136. Kolossow. *Zeitschr. f. wiss. Mikrosk.* ix. Hft. 1 and 3.—137. Rindfleisch. *Pathological Histology.* Transl. Baxter. New Syden. Soc. 1872, i. 92.—138. Ziegler. The various editions of his *Allgemeine Pathologie* give the literature of this discussion up to date. His general articles upon Inflammation (*Ziegler's Beitr.* 1892, xii. and *Twentieth Century Practice of Medicine*, New York, 1899) deserve study.—139. Wharton Jones. *Phil. Trans.* 1846, 64.—140. Lister (Lord). *Phil. Trans.* 1858, cxlviii. 678.—141. Weber. Quoted by Lister (140).—142. Ryneck. *Rollett's Untersuchungen*, 1870, 103.—143. Addison, W. *Exptl. and Pract. Researches upon Infl.* London, 1843.—144. Waller, Aug. *Phil. Mag.* 1846, xxix. 217, 298, 397.—145. Dutrochet. *Recherches anat. et physiol. sur la structure interne des anim.*, etc., Paris,

1842, 214.—146. Martin, Sydney. *Lectures on General Pathology*, London and Philadelphia, 1904.—147. Lavdowsky. *Virchow's Archiv*, 1884, xcvii. 177.—148. Binz. *Virchow's Arehiv*, 1874, lix. 293; *ibid.* 1878, lxxiii. 282; *ibid.* 1882, lxxxix. 389. —149. Disselhorst. *Virchow's Archiv*, 1888, cxiii. 108.—150. Bouchard. "Essai d'une Théorie d'Infection," *Verhandl. d. X. Internat. Med. Congr.* Berlin, 1890.—151. Roger. *Contrib. à l'étude de l'immunité acquise*, p. 1.—152. Charrin. *Verhandl. d. X. Internat. Med. Congr.* Berlin, 1890, ii. part 3, p. 29.—153. Ruffer. *Ann. de l'Instit. Pasteur*, 1891, v. 673; *Brit. Med. Journ.* 1890, i. 1177.—154. Sidler. *Diss.* Zurich, 1895.—155. Mall. *Arch. f. Anat. u. Physiol.* Physiol. Abth., Suppl. Bd., 1890, 57.—156. Klebs. *Allg. Pathologie*, 1889, ii. 384.—157. Severini. *La contrattilita dei capillari*, 1881.—158. Gergens. *Pflüger's Archiv*, 1876, xiii. 591.—159. Rütimeyer. *Arch. f. exptl. Pathol.* 1882, xiv. 384.—160. Samuel. *Virchow's Archiv*, 1890, cxxi. 396.—161. Roger. *C. R. Soc. de Biol.* 1890, 222 and 646.—162. Meltzer and Meltzer. *Journ. of Med. Research*, 1903, x. 135; *Am. Journ. of Physiol.* 1903, ix. 57.—163. Head and Campbell. *Brain*, 1900, xxiii. 353.—164. Virchow. *Cellular Pathology*, Eng. Ed. transl. from 2nd edition by Chance, London and New York, 1879.—165. See MacCallum, W. G. *Johns Hopkins Hosp. Reps.* 1902, x. 375; *Journ. Am. Med. Assoc.* Sept. 3, 1904; see also Kretz. *Wiener klin. Wochenschr.* 1900, xiii. 271.—166. Baumgarten. *Ueber Tuberkel u. Tuberkulose*, i.; *Die Histogenese des Tuberkulosen-processes*, Berlin, 1885.—167. Weigert, C. *Gesammelte Abhandl*, Leipzig, 1906, i.—168. Levin, I. *Journ. Med. Research*, 1901, vi. 145.—169. Starling. *Croonian Lectures, Roy. Soc.* and *Lancet*, xx. 1905, ii.—170. Scheltema. *D. med. Wochenschr.* 1887, 463; Nikiforoff. *Ziegler's Beiträge*, 1890, viii. 419.—171. Krafft. *Ziegler's Beiträge*, 1. 1884.—172. Podwyssozki. *Ziegler's Beiträge*, 1884, i.—173. Coen. *Ziegler's Beiträge*, 1888, ii. 29 and 107.—174. Fischer. *Diss.* Tübingen, 1888.—175. Arnold. *Arch. f. mikr. Anat.* 1887, xxx. 205.—176. Marchand. *Ziegler's Beiträge*, 1888, iv.—177. Reinke. *Ziegler's Beiträge*, 1889, v. 439; Ziegler. *Allgem. Pathologie*, 10th edit. Jena, 1901, 380, gives good bibliography on this subject.—178. Sherrington and Ballance. *Journ. of Physiol.* 1889, x. 550; *Ctbl. f. Pathol.* 1890, i. 697.—179. Jürgenlünas. *Ziegler's Beiträge*, 1901, xxix. 92.—180. Tadei. *La fibre elastich. nei tessute di cicatrice*, Ferrara (A. Soati), 1903; Schiffmann. *Ctbl. f. Path.* 1903, xiv. 833; Katsurada. *Ziegler's Beiträge*, 1902, xxxi. 296.—181. Gilchrist. *Johns Hopkins Hosp. Repts.*

1896, i. 269 ; Gilchrist and Stokes. *Journ. of Exper. Med.* 1898, iii. 53 ; see also Hektoen. *Ibid.* 1899, iv. 261 ; Ricketts. *Journ. of Med. Res.* 1901, vi. 374.—182. Boyce. *Journ. of Path.* 1893, i. 164 ; see also Grawitz. *Virchow's Archiv*, 1880, lxxxi. 355 ; Leber (29).—183. Nicholls. *Studies from the Royal Victoria Hosp., Montreal*, 1902, i. No. 3 ; see also Kelly. *Am. Journ. Med. Sci.* 1903, cxxv. 116.—184. Martin, R. *Montreal Med. Journ.* 1896, xxiv. 860.—185. Adami. *On the Relationship between Inflammation and sundry Forms of Fibrosis* (Middleton-Goldsmith Lectures), *Med. Record* (*N.Y.*), 1896, 361, 397, 469, 505.—186. Jores, L. *Wesen u. Entwickelung der Arteriosklerose*, Wiesbaden, Bergmann, 1903.—187. Martin, C. F. *Trans. Assoc. Am. Phys.* 1905, xx.—188. Rolleston. *Diseases of the Liver*, Philadelphia, New York, and London. Saunders, 1905, 175.—189. Thoma. *Virchow's Archiv*, civ. and subsequent volumes ; *Ziegler's Beitr.* 1891, x.—190. Councilman. *Trans. Assoc. Am. Phys.* 1891, vi. 179.—191. Roy and Adami. *Brit. Med. Journ.* 1888, ii. 1321.—192. Filehne. *Proc. Physiol. Soc.* Cambridge, 1892 (apparently not published in the *Journ. of Physiol.*, although it is referred to in the *Virchow-Hirsch. Jahrbuch*).—193. Pasteur. *Bull. de l'Acad. de méd.* 1879, 1152.—194. Charrin. *La maladie pyocyanique*, Paris, 1889.—195. Roy and Cobbett. See Art. "Shock" in 1st edition of Allbutt's *System*, iii. 326 ; see also Sherrington and Copeman. *Journ. of Physiol.* 1893, xiv. 52 ; Lazarus Barlow. *Ibid.* 1894, xvi. xiii.—196. Crile. *An Experimental Research into Surgical Shock*, Philadelphia. Lippincott, 1899 ; see also Parascandolo, *Arch. de Physiol.* 1898, x. 188.—197. Rieder. *Beiträge z. Kenntniss. d. Leukocytose*, 1892.—198. Löwit. *Arch. f. mikr. Anat.* 1891, xxxviii. ; 1890, xxxvii. ; *Ziegler's Beiträg.* 1891, x. ; *Studien z. Phys. u. Path. der Blutes*, 1892.—199. Sherrington. *Proc. Roy. Soc.* 1894, lv.—200. Everard, Demoor, and Massart. *Ann. de l'Instit. Pasteur*, 1893, vii.—201. Welch. *Amer. Journ. of the Med. Sciences*, 1897, cxiii. 631.—202. Ruffer. *Brit. Med. Journ.* 1897, i. 1177.—203. Nicholls. *Journ. of Med. Research*, 1904, xi. 455.—204. Ford. *Journ. of Hygiene*, 1901, i. 277, with series of tables in *Trans. Assoc. Am. Phys.* 1900, xv. 389.—205. Wroszek. *Arch. polonaises d. sc. biol. et méd.* 1903, ii. 1796 (Ref. *Journ. de Physiol. et Path. gén.* 1904, vi. 385.—206. Adami. *Journ. Amer. Med. Assoc.* Dec. 23, 1899.—207. Harris, D. F. *Brit. Med. Journ.* 1900, ii. 741.

INDEX

THE END

Printed by R. & R. Clark, Limited, *Edinburgh.*